UNIVERSITY OF ALBERTA

Radical Cyclization onto Hydrazones and Oximes, and Studies on Radical Deoxygenation

by

Rajendra Subedi ©

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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Date: 30th October 2001

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Radical Cyclization onto Hydrazones and Oximes, and Studies on Radical Deoxygenation** submitted by **Rajendra Subedi** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

D. L. J. Clive

Dr. D. L. J. Clive

Martin Cowie

Dr. M. Cowie

Dr. D. Hall

Dr. O. Hindsgaul

Peter Sporns

Dr. P. Sporns

per (Chair)

30 Oct. 2001

Dr. R. Batey

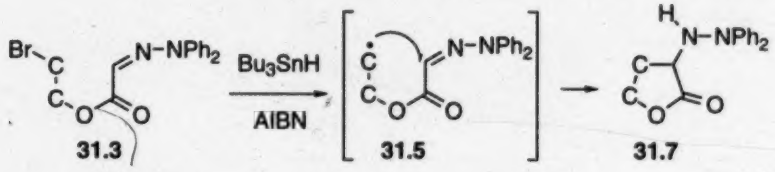
(External Examiner)

To

My family

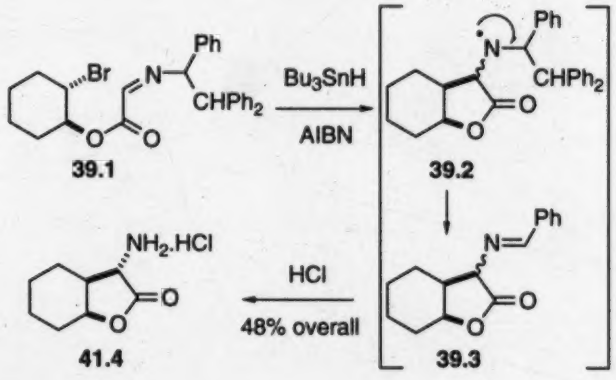
ABSTRACT

The first part of this thesis describes radical cyclizations involving imine and hydrazine acceptors. A general process was developed for construction of α-hydrazino lactones (such as **31.7**) by radical cyclization of the corresponding esters (such as **31.3**). Studies were conducted on the conversion of these hydrazino lactones into α-amino lactones, but such conversion is not general.



31.3 **31.5** **31.7**

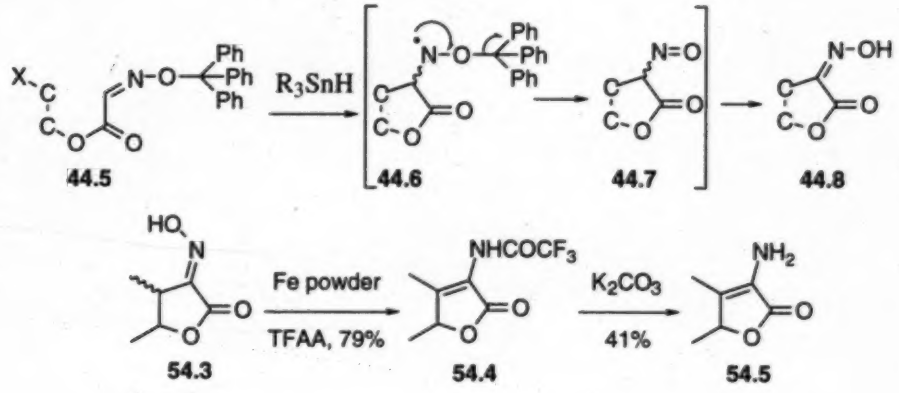
As a potential method of generating α-amino lactones by a route that does not involve hydrogenolysis, the radical cyclization of imino ester **39.1** was also examined.



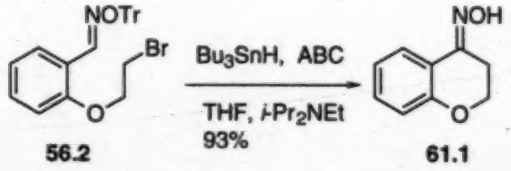
39.1 **39.2** **41.4** **39.3**

In the second part of this thesis I have developed a general method for construction of α-oximino lactones (such

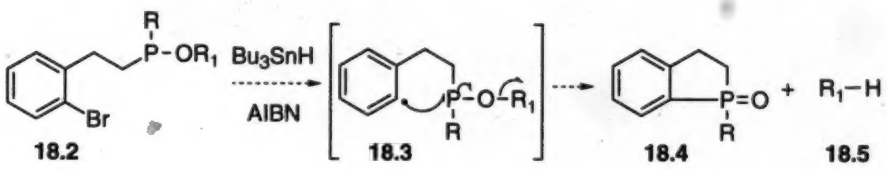
as **44.8**) by radical cyclization reaction of *O*-trityloximino esters (such as **44.5**). The special feature of this reaction is that the sp^2 status of the acceptor carbon is preserved; a result that is different from the one seen in the classical cyclization of hexenyl radicals or the radical cyclization of *O*-alkyloximes. The oximino lactones can be converted into enamides (e.g. **54.4**), and such a transformation was used to make the natural product **54.5**.



This reaction has been extended to non-lactone substrates (*e.g.* **56.2**), in which case we have studied the influence of various solvents and base additives. Among the various reaction conditions evaluated, use of THF as a solvent and diisopropylethylamine as an additive proved to be the most effective.



In the third part of the thesis attempts have been made to develop a new radical deoxygenation process involving trivalent phosphorus compounds along the lines of the sequence **18.2→18.5**.



18.2 **18.3** **18.4** **18.5**

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LIST OF ABBREVIATIONS

ABC.....1,1'-azobis(cyclohexanecarbonitrile)

Ac.....acetyl

AIBN.....2,2'-azobis(isobutyronitrile)

Bn.....benzyl

Boc.....*tert*-butoxycarbonyl

BPO.....benzoyl peroxide

t-Bu.....*t*-butyl

Bz.....benzoyl

CSA.....camphorsulfonic acid

DCC.....*N,N*-dicyclohexylcarbodiimide

DDQ.....2,3-dichloro-5,6-dicyano-1,4-benzoquinone

de.....diastereomeric excess

dr.....diastereomeric ratio

DMAP.....4-(dimethylamino)pyridine

DMECZ.....3,6-dimethyl-9-ethylcarbazole

DME.....1,2-dimethoxyethane

DMF.....dimethylformamide

DMSO.....dimethyl sulfoxide

DTBP.....di-*tert*-butyl peroxide

HMPA.....hexamethylphosphoric triamide

LDA.....lithium diisopropylamide

LUMO.....lowest unoccupied molecular orbital

MCZ.....*N*-methylcarbazole

MOM.....methoxymethyl

NBS.....*N*-bromosuccinimide

NMO.....4-methylmorpholine *N*-oxide

PCC.....pyridinium chlorochromate

Ph.....phenyl

Pr.....propyl

Py.....pyridine

TBAF.....tetra-*n*-butyl-ammonium fluoride

TBDPS.....*t*-butyldiphenylsilyl

TBS.....*t*-butyldimethylsilyl

TES.....triethylsilyl

TMS.....trimethylsilyl

Tf.....trifluoromethanesulfonyl

TFA.....trifluoroacetic acid

TFAA.....trifluoroacetic anhydride

THF.....tetrahydrofuran

THP.....tetrahydropyran

Tr.....triphenylmethyl

Ts.....*p*-toluenesulfonyl

Part 1

Radical Cyclization onto Hydrazones

I. Introduction

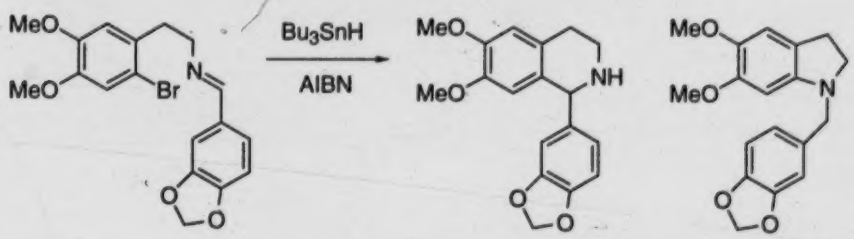
Radical reactions have emerged as a very useful synthetic tool in the construction of various ring structures. In the last decade new reagents and new precursors for the generation of radicals have been reported extensively.[1] Despite this intense interest, cyclizations, which are an important part of radical chemistry, are still at a stage where further developments are desirable. Recent research on radical cyclization has focused on the characteristics of radical acceptors that determine the regio- and chemoselectivities, and the factors that determine the stereochemistry of the product.[1] The ultimate goal of such studies is to be able to apply radical reactions in complex natural product synthesis. Numerous reviews on radical cyclizations have already been published, including theoretical studies and applications in organic synthesis.[1] My aim in this part of the thesis is to discuss the recent advances in radical cyclizations onto certain imines and hydrazone derivatives,[2] as this area is closely related to my research, which is described in the next chapter.

A. Radical cyclizations involving imine acceptors

Radical cyclizations involving imine acceptors have not been studied as extensively as is the case for other C=N acceptors. The most obvious reason for this is the difficulty in preparing or handling the precursor imines

because of their sensitivity to hydrolysis.

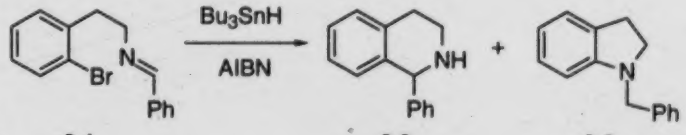
Takano[3] reported the earliest example of an intramolecular radical addition onto an imine double bond (Scheme 1). As a key step in the synthesis of cryptostyline alkaloids, the imine **1.1** was treated with Bu_3SnH and AIBN to give the 6-*endo* addition product **1.2** in 56% yield along with 10% of the 5-*exo* cyclization product **1.3**.



1.1 **1.2** (56%) **1.3** (10%)

Scheme 1

This type of 6-*endo* preference for cyclization of an aryl radical onto an imine acceptor has also been noted by Warkentin and Tomaszewski.[4] Thus, radical cyclization (Scheme 2) of **2.1** gave 6-*endo* product **2.2** and the 5-*exo* product **2.3** in the ratio of 12:1 (^1H NMR).

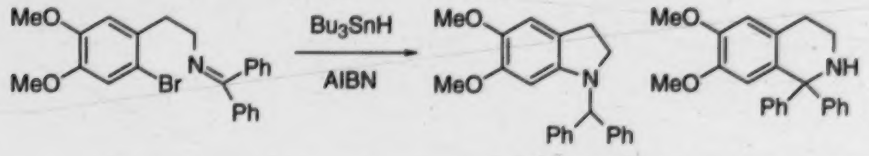


2.1 **2.2** **2.3**

Scheme 2

In contrast to the behavior of aldimine acceptors, Takano *et al.*[5] found that ketimines derived from acetophenone

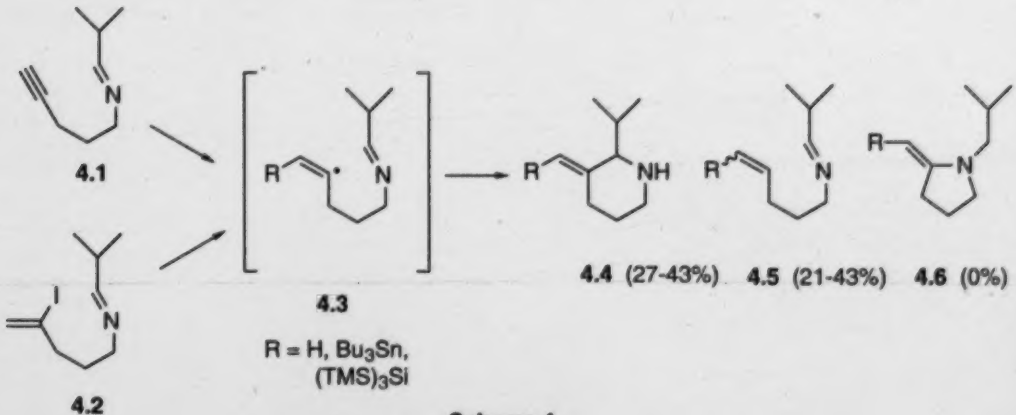
and benzophenone cyclized exclusively in a 5-*exo* fashion. Usually this pathway is kinetically disfavored but the extra steric hindrance present in **3.1** led to the exclusive formation of the indoline **3.2**.



3.1 **3.2** (59%) **3.3** (0%)

Scheme 3

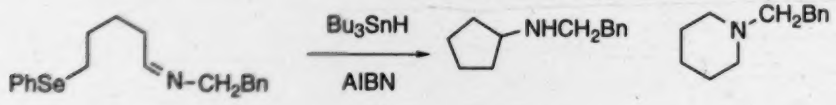
Komatsu and Ryu[6] have examined the question of regioselectivity; they studied the competition between 5-*exo* and 6-*endo* cyclization of vinyl radicals that were generated by heteroatom radical addition onto alkynes (Scheme 4). Addition of tributylstannyl or tris(trimethylsilyl)silyl radicals to alkyne **4.1** did not produce any 5-*exo* cyclization product **4.6**. Likewise, radicals generated from vinyl iodide **4.2** also failed to afford **4.6** (Scheme 4).



4.1 **4.2** **4.3** **4.4** (27-43%) **4.5** (21-43%) **4.6** (0%)

Scheme 4

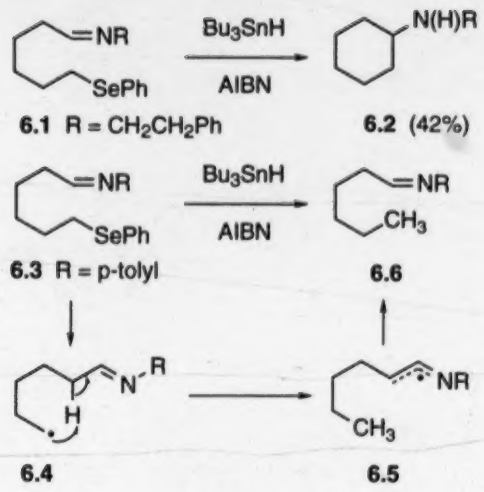
Extensive studies of radical cyclizations onto imine acceptors has been reported by Bowman and coworkers.[7] They have investigated the cyclization of various primary radicals generated from phenyl selenides onto the imine acceptors (Scheme 5). In a representative example, the cyclization of **5.1** gave the 5-*exo* product **5.2** (47%) and 6-*endo* product **5.3** (5%).



5.1 **5.2** (47%) **5.3** (5%)

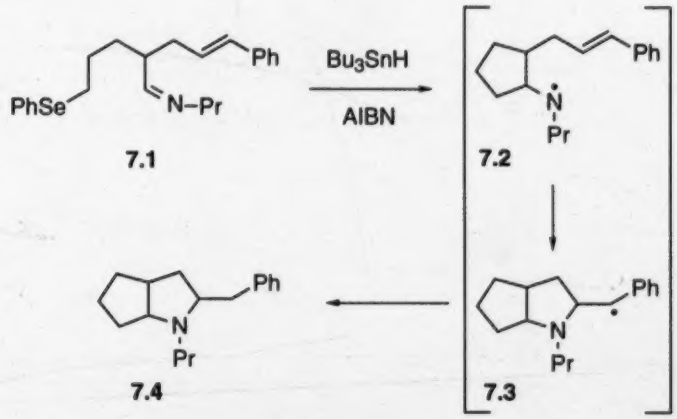
Scheme 5

A particularly interesting result was observed with imines **6.1** and **6.3** (Scheme 6). Radical cyclization[8] of **6.1** resulted in selective 6-*exo* closure (43%) rather than 7-*endo* closure, as expected. However, imine **6.3** gave only uncyclized material **6.6**. This outcome was attributed to the intervention of 1,5-hydrogen abstraction in the case of **6.3**, the abstraction being facilitated by the extra conjugation (see Scheme 6) of the resulting radical due to the presence of the aryl ring on nitrogen. The authors point out that this effect has been observed and proven[9] in the case of cyclization onto alkenes.



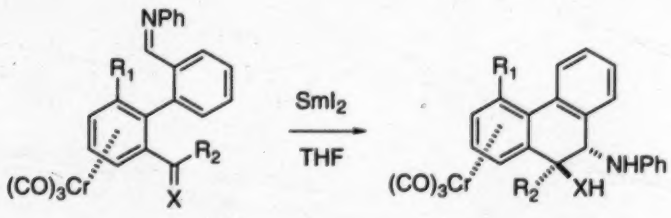
Scheme 6

Bowman *et al.*[10] have also developed the use of radical cyclization onto imines in cascade reactions. Thus, when imine **7.1** was treated with Bu_3SnH and AIBN, a 40% yield of the bicyclised product **7.4** was obtained (Scheme 7). In some cases, use of a Lewis acid has been shown to facilitate such cyclizations.



Scheme 7

Samarium iodide-induced cyclization onto the imine functionality was used to make enantiomerically pure *trans* amino alcohols, diols and diamines **8.2** by Uemura and coworkers.[11] The reactive functionalities were tethered to a optically active biphenyl-$Cr(CO)_3$ complex, and the observed product in each case was a single diastereomer with the NHPh and XH (X = O or NPh) groups in a *trans* relationship (Scheme 8). The chromium tricarbonyl moiety could be removed readily by photolytic decomplexation, and this step afforded various arenes of potential utility in asymmetric catalysis.



8.1 **8.2**

R_1 = H or OMe; R_2 = H or Me
X = O or NPh

75-86% yield
Single diasteromers

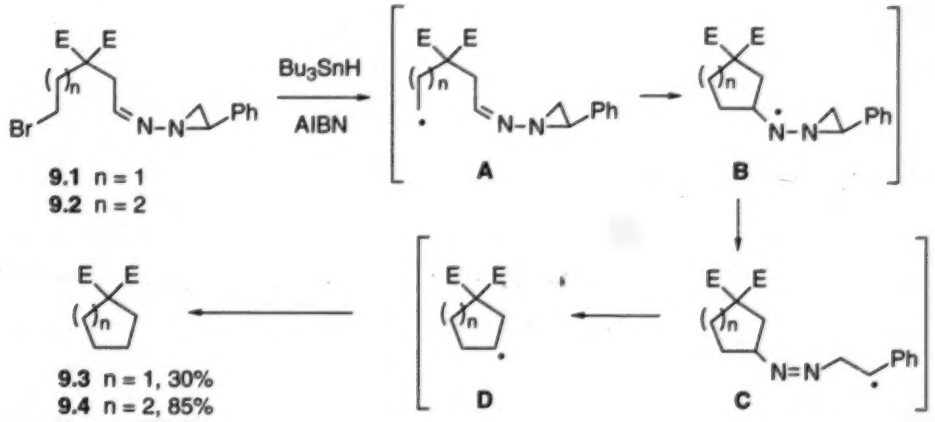
Scheme 8

B. Radical cyclization reactions involving hydrazone acceptors

Compared to imines, hydrazones are much less susceptible to hydrolysis or oxidations and thus are more popular substrates for radical cyclizations. However, until recently hydrazones have received much less attention as radical substrates than the corresponding oximes.

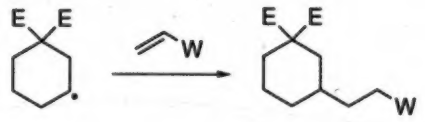
The first example of radical cyclization onto a

hydrazone was published in 1991 by Kim *et al.*[12] A unique hydrazone, derived from 2-phenylaziridinyl amine, was used as the radical acceptor (Scheme 9). When bromide **9.1** was treated with Bu_3SnH the initial radical **A** added to the imine double bond to generate an α-aziridinyl aminyl radical **B**. This intermediate radical then underwent ring opening to a stabilized benzyl radical **C**. Intermediate **C** then rapidly fragmented with the expulsion of nitrogen and formation of styrene. For the 5-*exo* cyclization **9.1** (n = 1) the yield was only 30%, but for the 6-*exo* addition, using **9.2** (n = 2), it was improved to 85%.



Scheme 9

The intermediate cyclohexyl radical produced in the above reaction can also be trapped with acrylonitrile and methyl acrylate (Scheme 10).

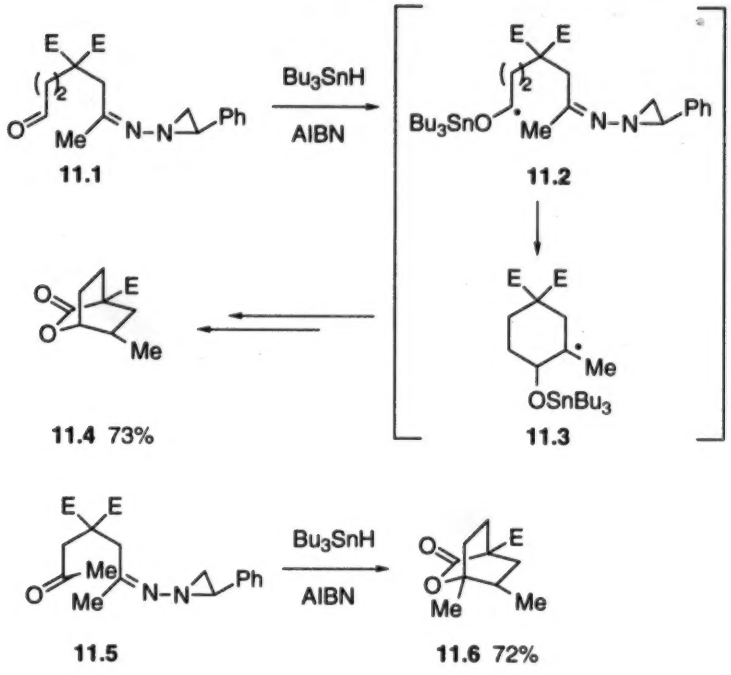


10.1 **10.2** W = CN, 86%
10.3 W = COOMe, 87%

Scheme 10

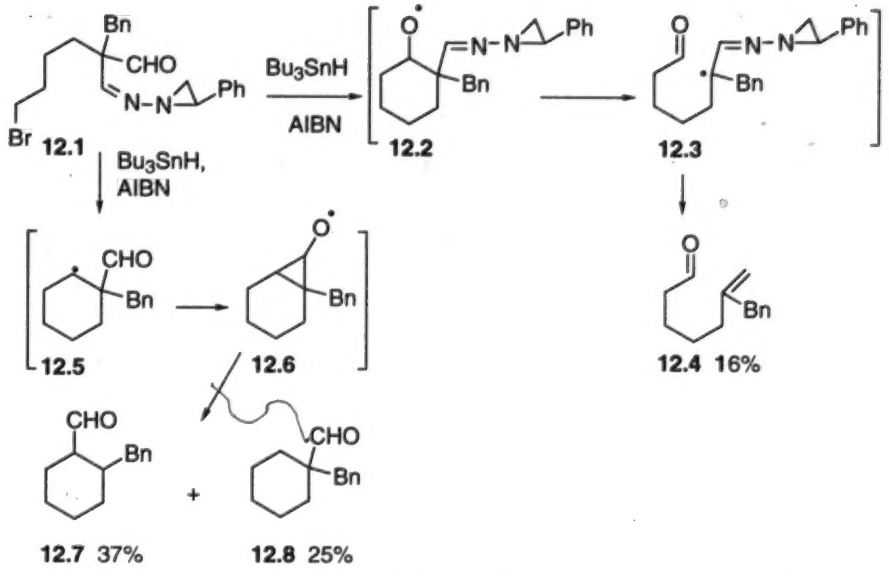
This type of reaction also proceeds well with keto hydrazones and is not limited to bromides as the source of radicals; alternative radical precursors such as phenyl selenides and acetylenes can also be used.

In order to expand the potential of the *N*-aziridinyl imino group as a radical acceptor, Kim *et al.*[13] have studied the competition between carbonyl and hydrazone groups as acceptors for stannyl radicals. The preferred pathway for **11.1**, in the competition between a keto-hydrazone and an aldehyde carbonyl, involved initial attack at the aldehyde (Scheme 11). The carbon-centered radical **11.2** generated by this addition then cyclized onto the C=N double bond to form the secondary radical **11.3**, after losing nitrogen and styrene. Subsequent reduction and lactonization afforded **11.4**. A similar preference was observed in the methyl ketone series, in which conversion of **11.5** into **11.6** was observed.



Scheme 11

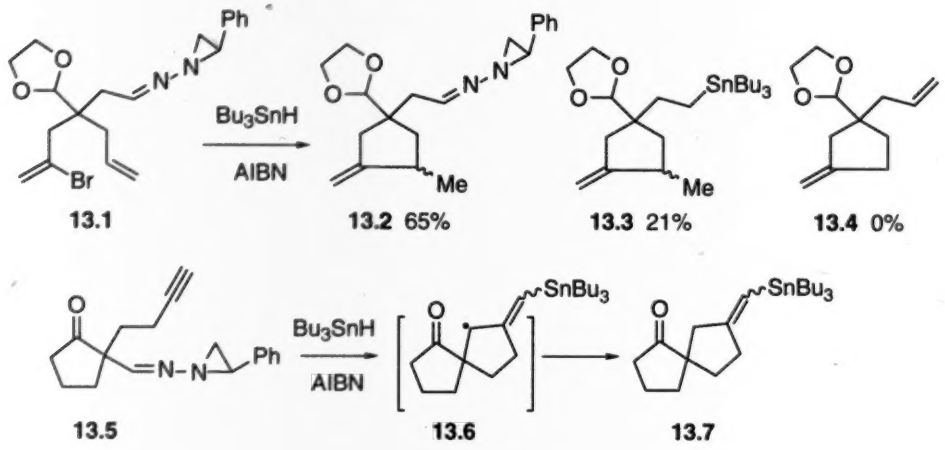
However, a more complex result was observed (Scheme 12) when a carbon-centered radical, generated by initial attack of stannane on a bromide, had the possibility of adding onto a formyl group or the C=N bond of the hydrazone. Thus, **12.1** afforded 16% of the aldehyde **12.4**, resulting from attack of the initial carbon-centered radical onto the aldehyde, followed by ring opening to **12.3** and expulsion of the *N*-aziridinyl moiety (Scheme 12). The competing pathway of addition of the initial radical to the hydrazone predominated, and afforded a 37% yield of **12.7** from rearrangement of **12.6**, as well **12.8** (25%), from quenching of **12.5**.



Scheme 12

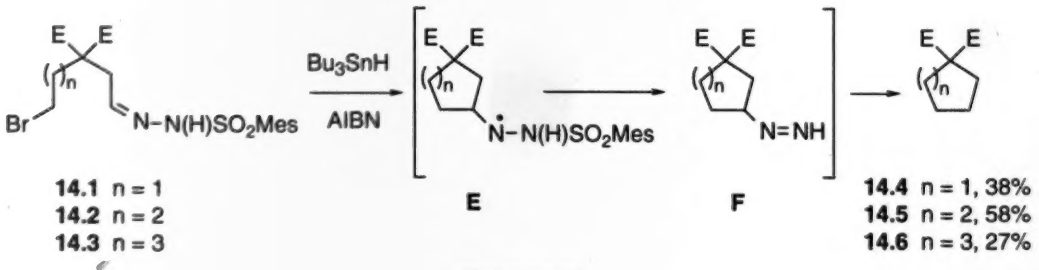
Competition between a C=C double bond and the C=N bond of hydrazones has also been studied.[13] In this case (see **13.1→13.2**) the alkene proved to be a better radical acceptor than the *N*-aziridinyl imino function. With 1.1 equivalents of Bu_3SnH, a mixture of **13.2** and **13.3** was obtained, and there was no evidence that any of the diene **13.4** was produced (Scheme 13). When the quantity of Bu_3SnH was increased to 2.2 equivalents, the stannane **13.3** was obtained in 80% yield as the only product. This compound resulted from addition of Bu_3SnH to the imino group in **13.1**. The situation was altered again when the competition was between a cyclopentanone carbonyl and the imino group. The vinyl radical derived from stannyl radical addition to the triple bond of acetylene **13.5** added preferentially to the

hydrazone to afford the spiro diquinane **13.7** in 85% yield.



Scheme 13

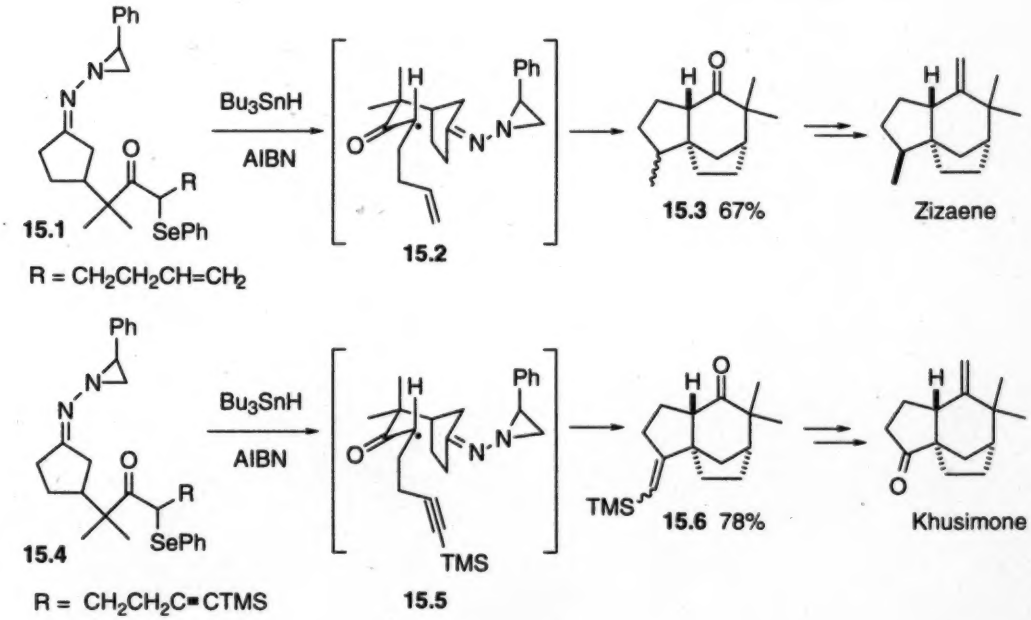
Kim and coworkers[14] have also studied arenesulfonyl hydrazones as radical acceptors (Scheme 14). The initially formed radicals **E** undergo β-elimination to expel the arenesulfonyl group so as to give the diazenes **F**. Extrusion of nitrogen from these intermediates then leads to the final products. Thus, depending on the chain length, simple 5-, 6- or 7-membered rings can be synthesized by this method.



Scheme 14

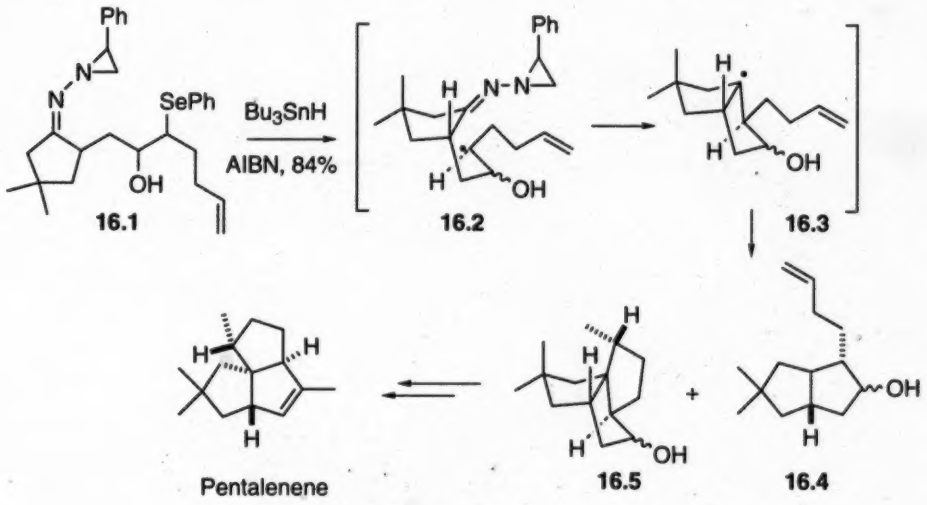
Kim[15] has reported formal syntheses of the

sesquiterpenes zizaene and khusimone by the use of the *N*-aziridinyl imine approach (Scheme 15). Relative configurations of the two new asymmetric centers were established in a single transformation involving radical cyclization of α-selenoketone **15.1** via a chairlike conformation **15.2**, then fragmentation and loss of styrene and nitrogen to generate a new carbon-centered radical. Tandem cyclization onto the alkene side chain led to **15.3**, which completed the formal synthesis of zizaene. Radical cyclization onto an alkyne side chain, as present in **15.4**, provided the *exo*-methylene analog **15.6**, which was further manipulated to complete a formal synthesis of khusimone.



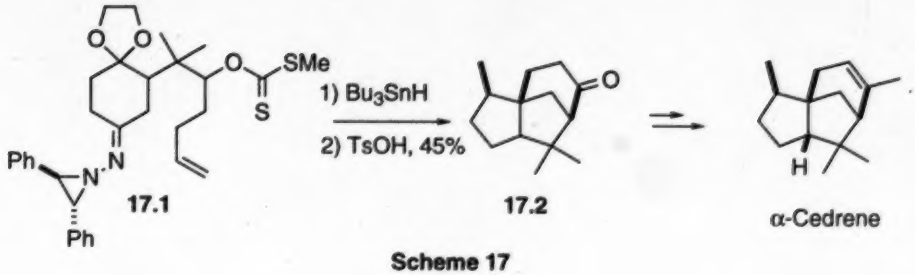
Scheme 15

This tandem strategy for construction of tricyclic compounds has also been applied[16] to a total synthesis of pentalenene (Scheme 16). In this approach, β-hydroxy selenide **16.1** was used as a radical precursor, leading to tricyclic alcohol **16.5** in a 6:1 ratio with minor bicyclic product **16.4**. Further chemical manipulation of the major product **16.5** completed the total synthesis of pentalenene.



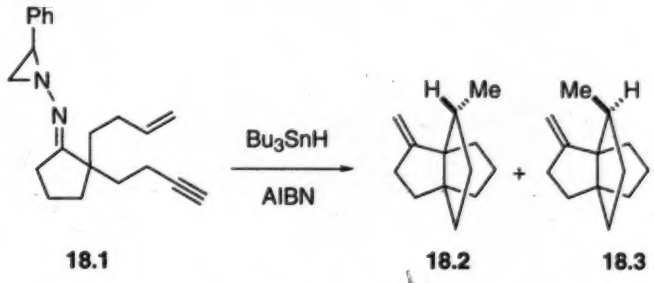
Scheme 16

The *N*-aziridinyl imine approach has also been used in a short and elegant synthesis of α-cedrene.[17] A xanthate precursor (**17.1**) was used, which underwent homolysis and 5-*exo* cyclization onto the C=N acceptor (Scheme 17). Fragmentation with loss of stilbene, then a second 5-*exo* cyclization onto the C=C bond gave the cedrene framework **17.2**, which was converted into α-cedrene in three steps.



Scheme 17

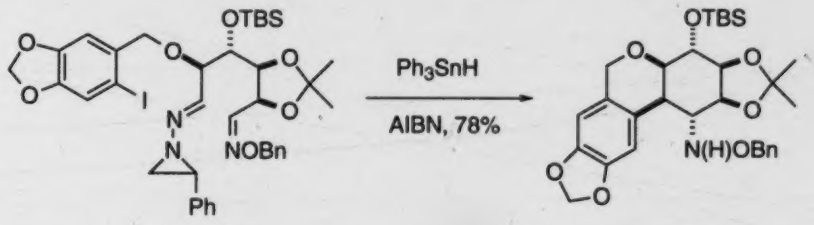
In a formal total synthesis of (±)-modhephene,[18] *N*-aziridinyl imine **18.1** has been used in a tandem radical cyclization to produce the intermediates **18.2** and **18.3** in a 9:1 ratio (74%). Compound **18.2** contains the required [3.3.3] propellane skeleton. Further manipulation of **18.2** completed the formal synthesis of (±)-modhephene (Scheme 18).



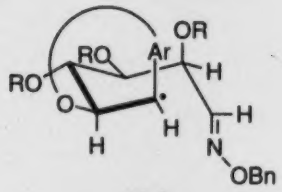
Scheme 18

In a synthesis of (+)-7-deoxypancratistatin, Keck[19] has also used *N*-aziridinyl imines for tandem radical cyclization (Scheme 19). When the iodide **19.1** was treated with Ph_3SnH and AIBN the desired cyclization product **19.2** was obtained in 78% yield as a single isomer. The stereochemistry of the nitrogen substituent was explained by a six-membered transition state model **19.3**, as shown in Scheme 19. Among

the two possible orientations of the oxime ether with respect to the adjacent oxygen substituent (syn or antiperiplanar), the antiperiplanar arrangement would be preferred so as to minimize non-bonded interactions in the transition state. Such a conformation leads to the observed product.



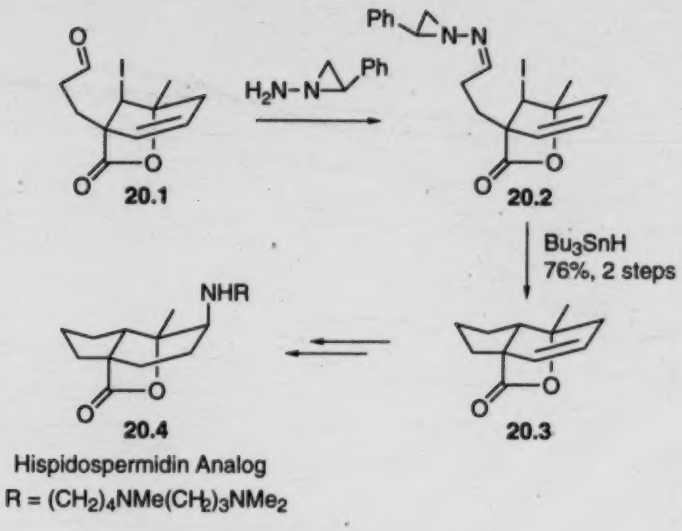
19.1 19.2



19.3

Scheme 19

Hart[20] has recently reported the use of the *N*-aziridinyl imine methodology in a synthesis of a *trans*-fused perhydroindan related to hispidospermidin (Scheme 20). In this case the approach has been used to form only one C-C bond. Radical cyclization of **20.2** and subsequent loss of nitrogen was followed by quenching by tin hydride to give the product **20.3**. This was then converted into the hispidospermidine analog **20.4** in several steps.

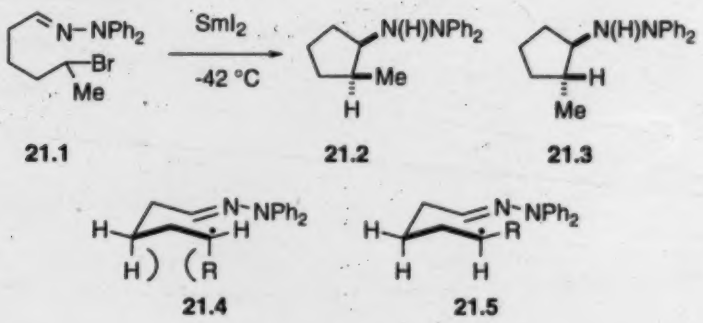


Scheme 20

The radical cyclization of *N*-aziridinyl imines has obviously introduced a new approach for the formation of five- and six-membered rings. However, this method does not retain the versatile nitrogen functionality due to the expulsion of nitrogen.

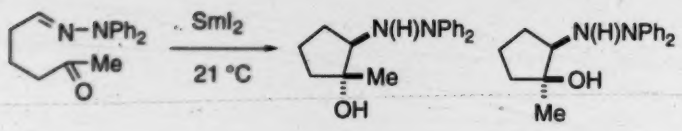
Fallis and Sturino[21] have demonstrated that *N,N*-diphenylhydrazones are efficient radical acceptors and thus can be employed in the construction of five and six membered ring structures with retention of the useful nitrogen functionality. Treatment of the bromomethyl ketone **21.1** with tributyltin hydride at 80 °C resulted in **21.2** and **21.3** in 95% yield and in a 2:1 ratio. With samarium diiodide and HMPA as an additive the same ratio was obtained in 91% yield at 21 °C. However, with SmI_2 and HMPA the diastereoselectivity increased as the temperature was

lowered. At -42 °C with samarium iodide, cyclic hydrazines were isolated in 88% yield and consisted of **21.2** and **21.3** in a ratio of 7:1 (Scheme 21). When the reaction was done at -78 °C with the iodide precursor the ratio increased to 11:1. The stereochemical preference has been explained by chairlike transition-state models. Thus cyclization from **21.5** is favored due to the avoidance of the diaxial interaction present in **21.4**.



Scheme 21

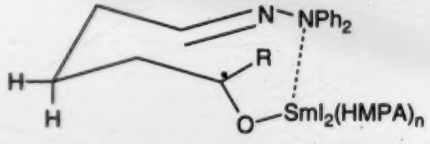
However, this trend of increasing stereoselectivity with decrease in temperature for the halide examples was reversed in carbonyl hydrazone systems, where the ratio increased at higher temperature, and good selectivities could be obtained under these conditions. Thus, when **22.1** was treated with samarium iodide, cyclized products **22.2** and **22.3** were obtained in 63% yield and in a 25:1 ratio at 21 °C (Scheme 22).



22.1 **22.2** **22.3**

Scheme 22

The authors[21] have explained the stereoselectivity in this reaction as arising from a nine-membered chelate of the type shown in **23.1** (Scheme 23), in which the bulky *N,N*-diphenylamino substituent adopts a pseudoequatorial conformation, and the pseudoaxial oxygen helps reduce the 1,3-nonbonded interactions experienced by the group R when it is axial.



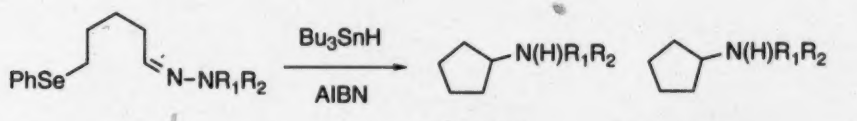
23.1

Scheme 23

The rate constants for 5-*exo* and 6-*exo* cyclizations of *N,N*-diphenylhydrazones have also been measured by Fallis.[22] They have found that the rate constants for the 5-*exo* cyclizations onto hydrazones are 200 times faster than corresponding 5-*exo* closures onto alkenes. In the case of the 6-*exo* process the rates are 100 times faster for hydrazones compared to the corresponding alkenes.

The effect of different substituents in the hydrazone acceptor has been studied by Bowman and coworkers.[7] When the

imine nitrogen was rendered more electropositive by attaching electron-withdrawing groups to it, the yield increased considerably. The *N*-phenylhydrazone **24.1** (R_1 = H, R_2 = Ph) gave **24.2** in only 18%, but the yield was improved to 60% with the urea system (R_1 = H, R_2 = $CONH_2$), giving **24.3** (Scheme 24).

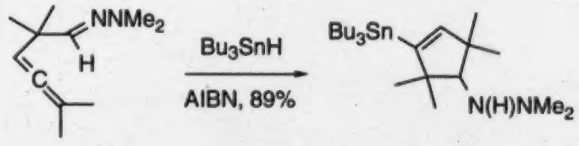


24.1 **24.2** 18% **24.3** 60%

R_1 = H, R_2 = Ph R_1 = H, R_2 = $CONH_2$

Scheme 24

Hatem *et al.*[23] have studied the radical cyclization of β-allenic *N,N*-dimethylhydrazones (Scheme 25). With aldehyde hydrazones such as **25.1**, hydrostannylation afforded the expected tertiary radical due to addition to the digonal center, and the resulting radical then cyclized to give the cyclopentene **25.2** via a 5-*exo* mode in 89% yield.

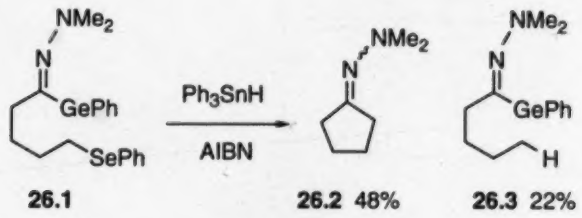


25.1 **25.2**

Scheme 25

Curran and coworkers[24] have reported that acylgermane dimethylhydrazone selenides, such as **26.1**, could be cyclized

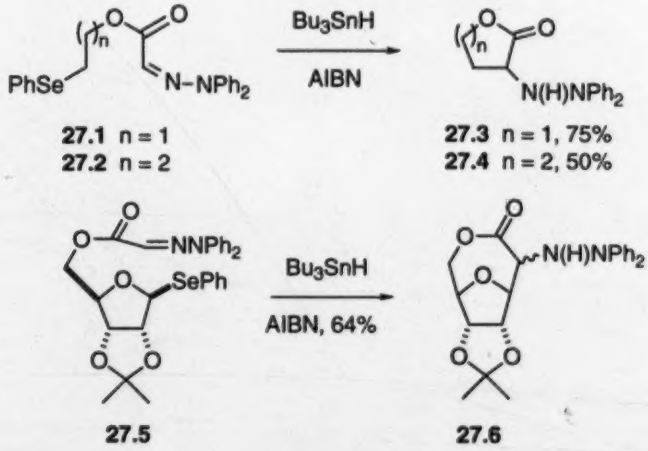
to hydrazone **26.2** only in a modest yield (48%), due to competitive reduction of the starting material, as shown in Scheme 26.



26.1 **26.2** 48% **26.3** 22%

Scheme 26

Clive and Zhang[25] have prepared α-amino lactones from *N,N*-diphenylhydrazone esters (Scheme 27). The yields of γ-lactones resulting from 5-*exo* cyclization are high, but for the 6-*exo* cyclization the yield of the lactone is decreased. An example of 7-*exo* ring closure, using a ribose-derived selenide, has also been reported. Thus, compound **27.5** cyclized to give a tricyclic system in 64% yield.



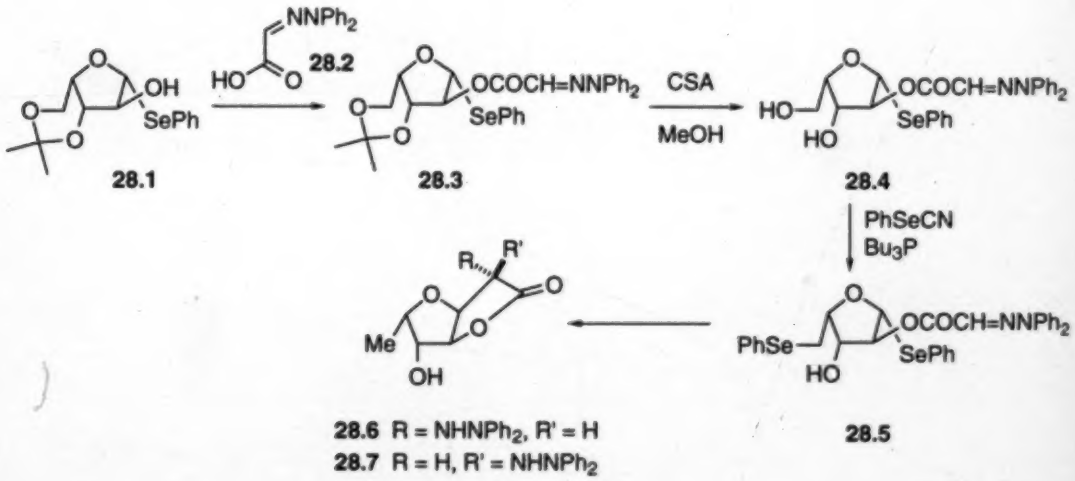
27.1 n = 1
27.2 n = 2

27.3 n = 1, 75%
27.4 n = 2, 50%

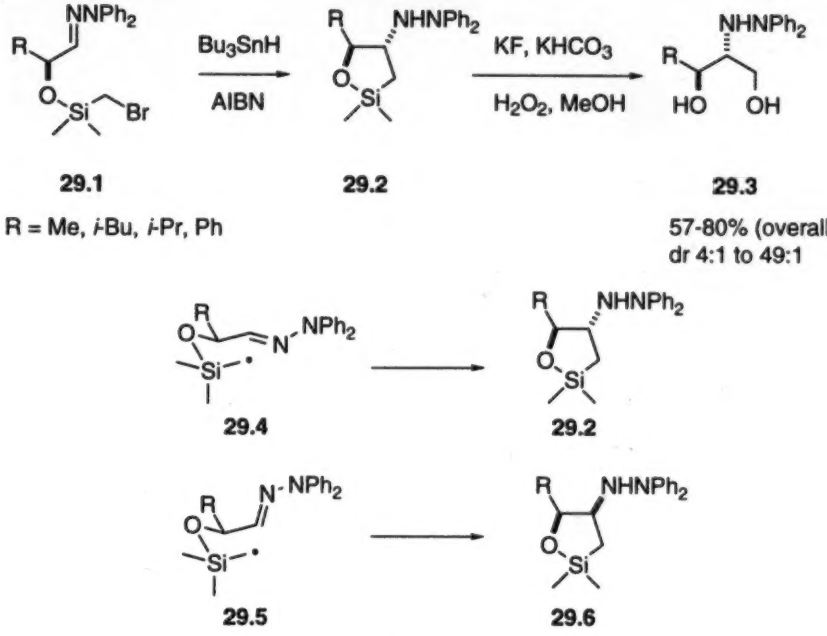
27.5 **27.6**

Scheme 27

Zhang and Clive[26] have extended this reaction to the synthesis of the antibiotic (+)-furanomycin. Alcohol **28.1** was coupled with (2,2-diphenylhydrazono)acetic acid **28.2** to give the hydrazono ester **28.3** in 95% yield. Although radical cyclization could have been performed at this stage, they decided to delay the process so that another radical reaction i.e. the deoxygenation at C(5) of the ribose unit could be performed at the same time as the required ring closure. Thus, selenide ester **28.3** was deprotected in order to liberate the two hydroxyls. The primary hydroxyl in **28.4** was selectively replaced by a PhSe-group to afford the required bis-selenide, and the radical cyclization was performed on this substrate. Cyclization and deselenation at C(5) occurred in one experimental operation to give 42% yield of **28.6** and 37% yield of **28.7**. Further manipulation of compound **28.6** led to (+)-furanomycin.

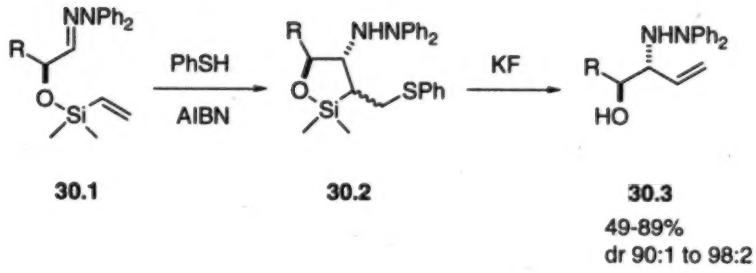


Friestad[27] has recently reported the cyclizations of silicon-tethered radicals onto hydrazones, after which the tether may be removed to afford acyclic products. The sequence occurs with useful and predictable stereocontrol. Chiral hydrazones **29.1** were prepared from the corresponding α-hydroxy aldehydes. Radical cyclization, followed by Tamao oxidation, afforded anti 2-hydrazino-1,3-diols **29.3** with good to excellent stereocontrol (Scheme 29). The stereochemical control was thought to have arisen in accordance with the Beckwith-Houk model,[28] which predicts enhancement of diastereoselectivity upon increasing substituent steric demand in 4-substituted 5-hexenyl radical cyclizations. A preferred chair-equatorial transition state **29.4** with a pseudoequatorial substituent (R), results in the observed product. The minor syn product would be expected from the disfavored chair-axial conformation **29.5**.



Scheme 29

A tandem addition-cyclization version of the above process has also been investigated by Friestad[29] (Scheme 30). Using thiophenol and AIBN, 5-*exo* cyclization of **30.1** occurred readily, and the silicon tether was removed in the same vessel by desilylation and concomitant β-elimination of benzenethiolate. Thus, chiral substituted vinylglycinol building blocks **30.3** were constructed with high diastereoselectivity.



30.1 **30.2** **30.3**

49-89%
dr 90:1 to 98:2

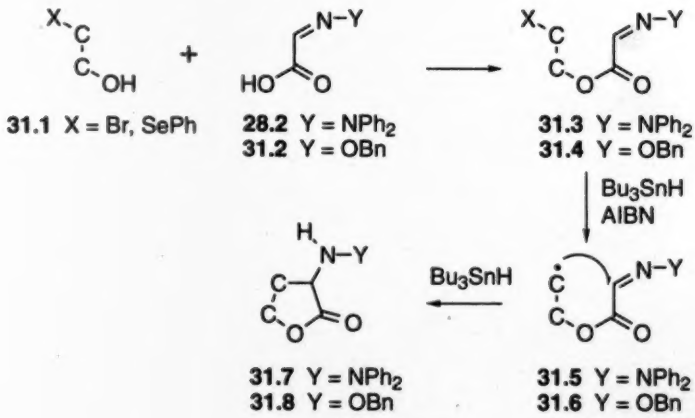
Scheme 30

C. Conclusions

In summary, hydrazones are versatile radical acceptors for a variety of situations, and hydrazones have been studied in more detail than imines. Further advances and new insights into all these reactions, and more sophisticated synthetic applications, will undoubtedly be seen in the future.

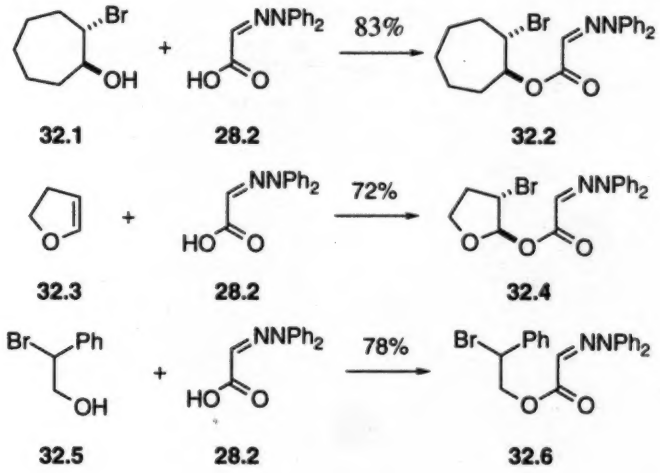
II. Results and Discussion

Preparation of carbocycles by addition of a carbon radical onto the carbon-nitrogen double bond of diphenylhydrazones has been explored in detail,[21,22] as described in the previous section. Later, it was discovered that such cyclizations proceeded smoothly for esters.[25] This process results in lactones in which the α-position carries nitrogen functionality, and the compounds can be converted into various natural and unnatural amino acids. In general, it was found that glyoxylic acid diphenylhydrazones **28.2** and the corresponding *O*-benzyloxime **31.2** could be esterified in high yield by β-bromo or phenylseleno alcohols **31.1**, and the resulting esters underwent radical cyclization to α-(2,2-diphenylhydrazino)- or α-[(phenylmethoxy)amino]lactones **31.7**/**31.8** on treatment with tributyltin hydride (Scheme 31).



Scheme 31

It was decided to expand the range of substrates which would give different types of unnatural amino acids, and my research was directed to this end. The precursors for the radical cyclization, which are shown in Scheme 32 were made in a similar fashion to that used in the earlier work, i.e. by coupling of the corresponding alcohol with the diphenylhydrazone reagent **28.2** (Scheme 32), except for compound **32.4**, which was made by adding NBS to a mixture of 4,5-dihydrofuran **32.3** and the diphenylhydrazone reagent (Scheme 32).



32.1 **28.2** **32.2**

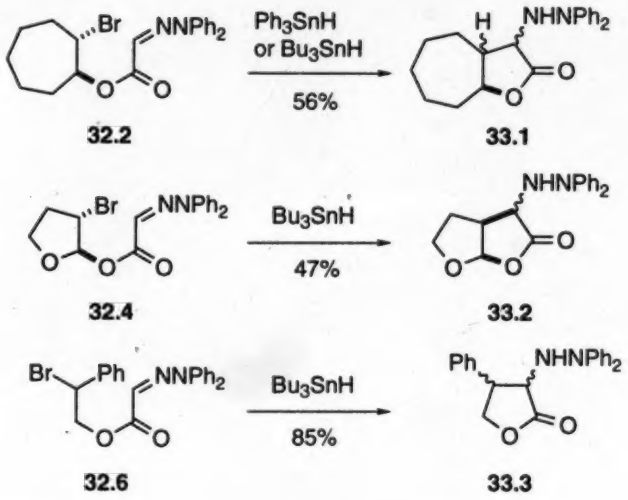
32.3 **28.2** **32.4**

32.5 **28.2** **32.6**

Scheme 32

Radical cyclization was conducted by simultaneously adding toluene solutions of Bu_3SnH and AIBN by double syringe pump to a refluxing solution of the substrate in the same solvent. At the end of the addition, refluxing was continued for an arbitrary period (generally 2-3 h). In one of the cases (formation of compound **33.1**, Scheme 33), Ph_3SnH was

tried in order to make a comparison with the aliphatic stannane, but without any significant influence on the result.



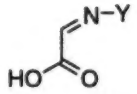
Scheme 33

Where the newly-formed ring is produced on an existing cyclic structure, the ring fusion geometry[30] is *cis* for [3.3.0] system (**33.2**), but both *cis* and *trans* ring-fused products are formed in the case of the [5.3.0] bicycle (**33.1**). The acyclic starting material **32.6** gave an isomer mixture, and for the *cis* ring-fused products both epimers at the α-position to the carbonyl were obtained with little, if any, selectivity. In the case of **33.3**, individual isomers could be separated, while in the case of **33.1**, among the four possible isomers, only one of them was separable in pure form (Scheme 33).

In principle, hydrogenolysis of the α-diphenylhydrazino

lactones or opening of the lactone products and hydrogenolysis of the N-N single bond should afford amino acids. But, in practice, this transformation was not straightforward. Only in the case of one of the simple lactones,[31] was hydrogenolysis successful in giving the α-amino lactone (as its hydrochloride salt).[31] In general, however, hydrogenolysis of 2,2-diphenylhydrazino lactones are reported to be unsuccessful.[32]

My aim was, therefore, to find a range of reagents which would undergo the cyclization as easily as or better than the diphenylhydrazino reagent and that would afford compounds that could be converted more easily into substances carrying an amino group. For this purpose, number of related reagents (Scheme 34) were prepared by the same process of condensation between glyoxylic acid and the appropriate amine derivative.

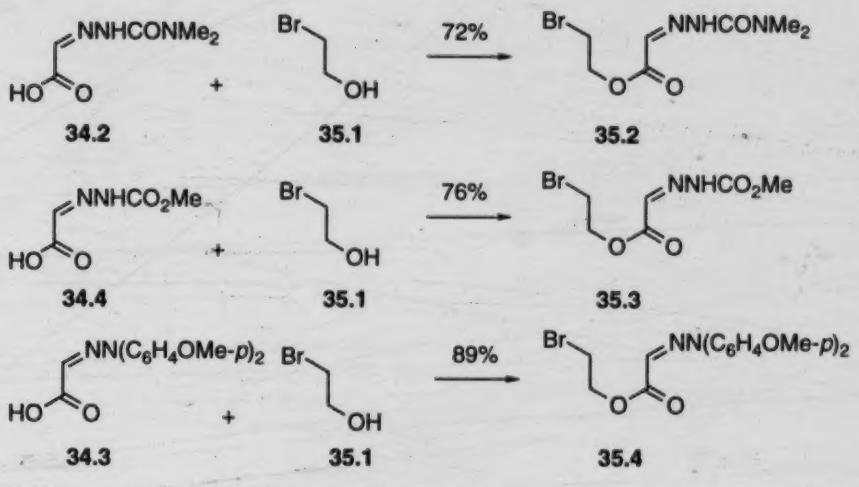


34.1 Y = $NHCONH_2$
34.2 Y = $NHCONMe_2$
34.3 Y = $N(C_6H_4OMe\text{-}p)_2$
34.4 Y = $NHCO_2Me$

Scheme 34

The corresponding esters were prepared by DCC-mediated coupling of the reagents with 2-bromoethanol (Scheme 35). The semicarbazone reagent **34.1** was too insoluble in common solvents (MeCN, DMF, EtOAc, CH_2Cl_2, acetone, sulfolane) for effective coupling with alcohols, but the other reagents

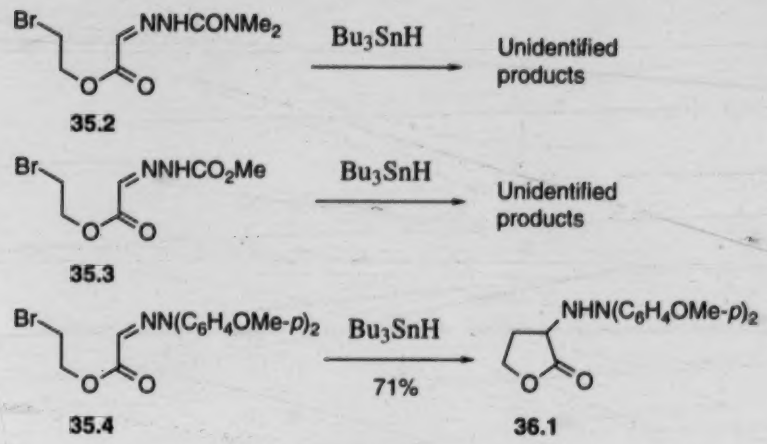
34.2, **34.3** and **34.4** could be coupled easily with alcohol **35.1**.



Scheme 35

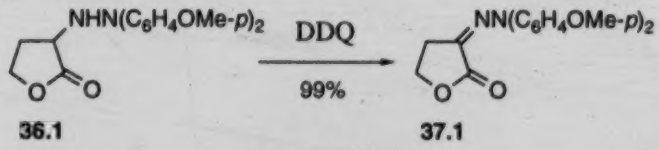
For one of the esters (**35.3**) we obtained an X-ray crystal structure. The data show that the C=N double bond has the *E* geometry, and all the atoms lie close to a plane, except for the bromine, which is perpendicular to the plane.

Radical cyclizations were conducted in the usual manner, using Bu_3SnH and AIBN (Scheme 36).



Scheme 36

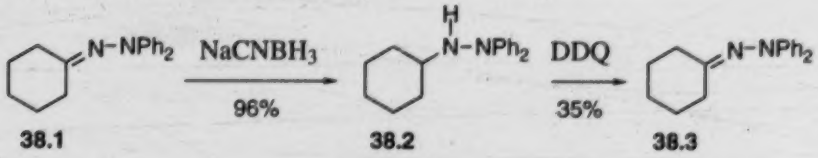
Radical reaction of **35.2** gave a mixture unidentifiable products, while in the case of **35.3** some of the starting material and a complex mixture were isolated. However, cyclization of **35.4** went smoothly to give the corresponding lactone **36.1** in 71% yield. We had hoped that removal of the *p*-methoxybenzene groups of compound **36.1**, by means of DDQ oxidation, would easily give the corresponding α-amino lactone. However, desaturation occurred more rapidly than oxidative removal of the *p*-methoxybenzene groups, and the α-hydrazono lactone **37.1**, rather than the product of simple dearylation, was isolated in quantitative yield (Scheme 37).



Scheme 37

In order to determine whether this is a general process

with hydrazines,[33] we explored this reaction a little further. Compound **38.1** was made by coupling diphenyhydrazine with cyclohexanone, and the compound was then reduced with sodium cyanoborohydride to afford **38.2** in 96% yield (Scheme 38). When compound **38.2** was treated with DDQ, only 35% of the expected hydrazone was obtained.

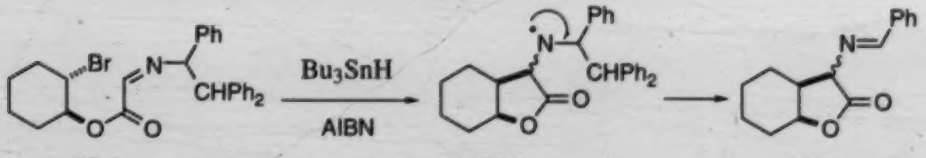


38.1 **38.2** **38.3**

Scheme 38

This result suggests that efficient desaturation by DDQ is possible only in the case of lactones, presumably because the electron withdrawing effect of the carbonyl increases the acidity of the α hydrogen.

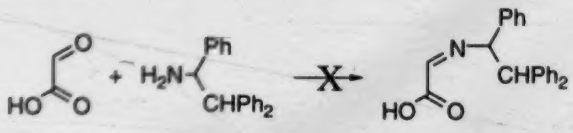
As a potential method of generating α-amino lactones by a route that does not involve hydrogenolysis, we decided to prepare ester **39.1**. This compound is so constituted that the initial radical cyclization intermediate **39.2** could lead directly to an imine (**39.3**), which would be expected to undergo easy hydrolysis (Scheme 39).



39.1 **39.2** **39.3**

Scheme 39

However, preparation of the required ester **39.1** was not straightforward. The usual procedure of DCC-mediated direct coupling of an alcohol with the acid reagent (see for example Scheme 35) was not possible, since we were unable to prepare the appropriate reagent **40.3** (Scheme 40). Thus, when an equimolar amount of glyoxylic acid **40.1** and amine **40.2** in CH_2Cl_2 were refluxed for 12 h in the presence of molecular sieves none of the desired product **40.3** was obtained.

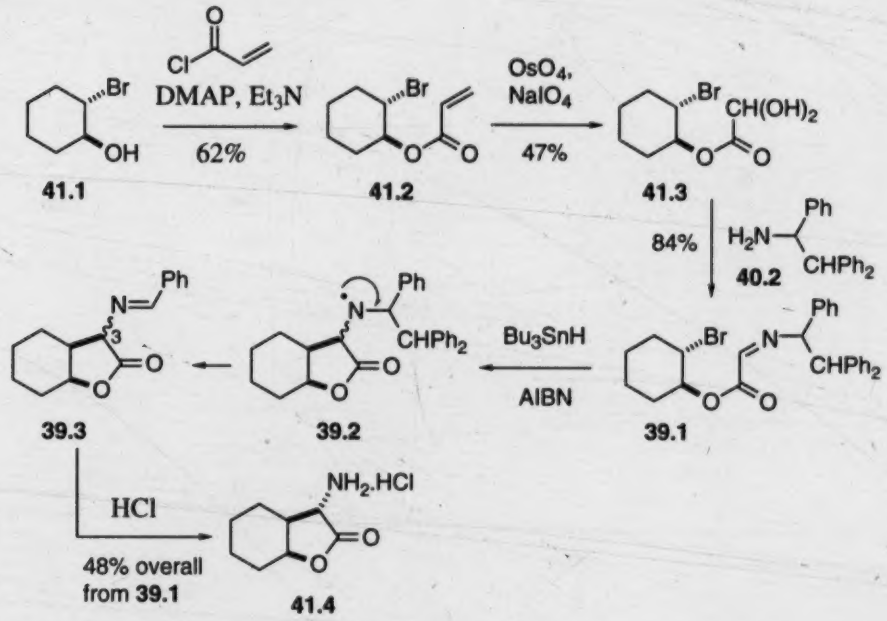


40.1 **40.2** **40.3**

Scheme 40

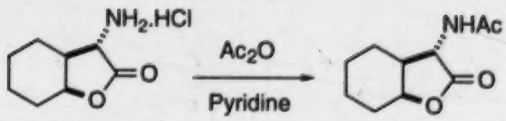
Therefore, the required ester **39.1** had to be prepared in an indirect way (Scheme 41). Bromocyclohexanol **41.1** was coupled with acryloyl chloride to give bromo ester **41.2** in 62% yield. This was then converted into **41.3** using OsO_4 and $NaIO_4$. The material was mainly the hydrate, but contained (^1H NMR) a small amount (ca 5 mol%) of the parent aldehyde. Imine **39.1** was then prepared by refluxing an equimolar amount of the corresponding amine **40.2** and the hydrate **41.3** in CH_2Cl_2 in the presence of molecular sieves. This imine was stable to silica gel chromatography, and could be purified and isolated in 84% yield. The imine obtained in this way was then subjected to our standard radical cyclization

conditions, using Bu_3SnH in the presence of AIBN. The crude product obtained from the cyclization reaction was directly treated with dilute hydrochloric acid. The resulting yellow powder was recrystallized from an EtOH-Et_2O mixture to give **41.4** in 48% overall yield as a single isomer.



Scheme 41

Due to the fact that the other isomer of **41.4** was not available, the stereochemistry of α-amino lactone **41.4** at C(3) relative to the necessarily *cis* ring junction could not be assigned by spectroscopic methods. However, the stereochemistry was tentatively assigned by making the acetamide derivative **42.1** (see Scheme 42), which was a known compound[34] and comparing the melting point with the reported value.



41.4 **42.1**

Scheme 42

Although **41.4** was obtained as a single isomer (after recrystallization), we assume by analogy with our other results, that the precursor **39.3** was a mixture of C(3) epimers. We did not attempt to generalize the cyclization-hydrolysis process shown in Scheme 41, however, as we were unable to prepare the reagent **40.3**, as discussed above; such a reagent would have given us access to esters of type **39.1** in a single step by coupling with bromo alcohols.

In summary, glyoxylic acid diphenylhydrazones are easily esterified in high yield with β-bromo alcohols. The resulting esters undergo radical cyclization to α-(2,2-diphenylhydrazino)lactones on treatment with tributyltin hydride. One ester for radical cyclization was also made using an enol ether. Several derivatives of glyoxylic acid were evaluated, but none was as effective as glyoxylic acid diphenylhydrazone. We have also demonstrated an example of an unusual radical displacement[35] of carbon that generates an imine.

III. Experimental section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[36] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic

acid,[37] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry THF was distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. HMPA was distilled from CaH_2 under reduced pressure (oil pump), and kept under Ar atmosphere over molecular sieves. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

FTIR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

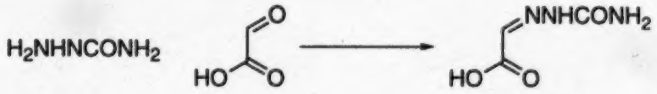
^1H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), Bruker AM-360 (at 360 MHz) or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively, which are assigned based on the APT experiment.

Mass spectra were recorded with AEI Models MS-12, MS-50 MS9 (modified), Kratos MS50 (modified) or Micromass ZabSpec Hybrid Sector-TOF mass spectrometers. For isotope peaks,

high-resolution mass data were taken from the highest mass number peak shown in the spectrum.

Compounds isolated by flash chromatography were pure by TLC and, unless otherwise stated, also as judged by high field ^{1}H and ^{13}C NMR spectra.

(Semicarbazono)acetic acid (34.1).



\- **40.1** **34.1**

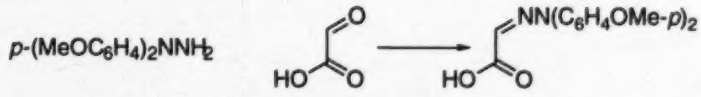
Semicarbazide hydrochloride (1.0 g, 8.9 mmol) and AcONa (1.5 g, 11 mmol) were dissolved in water (10 mL). Glyoxylic acid (0.50 g, 3.8 mmol) was added, the mixture was stirred for 30 min, and then left to stand for 2 h. The solvent was evaporated to afford a white solid. Recrystallization from absolute EtOH gave **34.1** (1.02 g, 72%): mp 231-232 °C; FTIR (Microscope) 3455, 2200-3350, 1705, 1661, 1611 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 6.75 (s, 2 H), 7.10 (s, 1 H), 10.9 (s, 1 H), 12.01-12.52 (br s, 1 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 129.3 (d'), 155.8 (s'), 164.3 (s'); exact mass *m/z* calcd for $C_3H_5N_3O_3$ 131.0331, found 131.0328.

[[(Dimethylamino)carbonyl]hydrazono]acetic acid (34.2).

\- **40.1** **34.2**

4,4-Dimethylsemicarbazide (2.565 g, 24.88 mmol) and glyoxylic acid monohydrate (2.29 g, 24.9 mmol) were dissolved in water (10 mL), and the solution was stirred at room temperature for 26 h (TLC control, 1:1 EtOAc-MeOH). Evaporation of the water at 40 °C gave **34.2** (3.498 g, 88%) as a crystalline solid, which was recrystallized from MeOH with 81% recovery: mp 186-189 °C; FTIR (Microscope) 3226, 3066, 1722, 1694, 1594, 1548 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 2.87 and 2.92 (two singlets, 6 H in all), 7.43 and 7.47 (two singlets, 1 H in all), 10.65 and 10.71 (two singlets, 1 H in all), 12.52-12.93 (br s, 1 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 36.2 (q'), 133.1 (d'), 153.9 (s'), 165.1 (s'); exact mass *m/z* calcd for $C_5H_9N_3O_3$ 159.0644, found 159.0640.

[Di(4-methoxyphenyl)hydrazono]acetic acid (34.3).

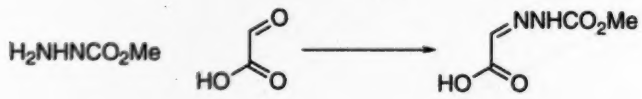


\- **40.1** **34.3**

Glyoxylic acid (0.8308 g, 9.025 mmol) was added to a stirred solution of amine (2.2034 g, 9.0258 mmol) in MeOH (15.0 mL), and stirring was continued overnight. Evaporation

of the solvent, and flash chromatography of the residue over silica gel (4 x 32 cm), using 60% EtOAc-hexane, gave **34.3** (2.3901 g, 88%) as a crystalline solid: mp 168-170 °C; FTIR (CH_2Cl_2 cast) 2953, 2836, 1682, 1652, 1604, 1539 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.85 (s, 6 H), 6.49 (s, 1 H), 6.89-7.17 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 55.6 (q'), 115.2 (d'), 121.9 (d'), 166.7 (s') (the number of signals is less than expected because of signal overlap); exact mass *m/z* calculated for $C_{16}H_{16}N_2O_4$ 300.1109, found 300.1108.

[(Methoxycarbonyl)hydrazono]acetic acid (34.4).



- **40.1** **34.4**

Methyl carbazate (1.8044 g, 20.039 mmol) and glyoxylic acid monohydrate (1.841 g, 20.01 mmol) were dissolved in water (10 mL), and the mixture was stirred. A solid started to precipitate within 1 h. Stirring was continued for 6 h, and the water was then evaporated at 40 °C to afford **34.4** (2.92 g, 100%) as a crystalline solid: mp 177-178 °C; FTIR (Microscope) 2300-3400, 1721, 1656, 1594 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 3.82 (s, 3 H), 7.30 (s, 1 H); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 52.5 (q'), 135.1 (d'), 153.6 (s'), 164.4 (s'); exact mass *m/z* calcd for $C_4H_6N_2O_4$ 146.0327, found 146.0325.

General Procedure for Coupling of Alcohols with

Reagents 28.2.

Glyoxylic acid diphenylhydrazone **28.2** (1.1 equivalent) was added to a stirred mixture of the alcohol (1.0 equivalent), DCC (1.1 equivalent) and DMAP (0.10 equivalent) in dry CH_2Cl_2. Stirring was continued for 12 h, and the mixture was then filtered. The insoluble material was washed with dry CH_2Cl_2 and the combined filtrates were evaporated to give a residue which was processed as described for the individual experiments.

General Procedure for Radical Cyclization.

The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The system was flushed with Ar for 5-10 min, and dry PhMe was injected into the flask. The solution was heated to 110 °C, and individual solutions of Bu_3SnH and AIBN in PhMe were injected simultaneously by syringe pump over 10 h. Refluxing was continued for an arbitrary period of 2 h after the addition. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

***Trans*-2-Bromocycloheptyl (Diphenylhydrazono)-acetate (32.2).**

32.1 **32.2**

The general procedure for coupling alcohols with **28.2** was followed, using **28.2** (168 mg, 0.0699 mmol), alcohol **32.1**[38] (150 mg, 0.776 mmol), DCC (158 mg, 0.765 mmol), and DMAP (8.5 mg, 0.069 mmol) in CH_2Cl_2 (5 mL). Flash chromatography of the crude product over silica gel (1.7 x 35 cm), using 10% EtOAc-hexane, gave **32.2** (243.0 mg, 83%) as light-yellow oil: FTIR (CH_2Cl_2 cast) 1726, 1700, 1590, 1493, 1457 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.52-1.90 (m, 7 H), 1.92-2.21 (m, 2 H), 2.22-2.40 (m, 1 H), 4.31 (dt, J = 7.9, 3.7 Hz, 1 H), 5.3 (dt, J = 7.8, 3.2 Hz, 1 H), 6.53 (s, 1 H), 7.18-7.52 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 22.6 (t'), 24.9 (t'), 27.9 (t'), 31.3 (t'), 35.2 (t'), 57.2 (d'), 80.3 (d'), 122.7 (d'), 124.3 (d'), 126.5 (d'), 130.3 (d'), 142.5 (s'), 163.5 (s'); exact mass m/z calcd for $C_{21}H_{23}{}^{81}BrN_2O_2$ 416.09225, found 416.09179.

***Trans*-3-Bromotetrahydrofuran-2-yl (Diphenylhydrazono)acetate (32.4).**

32.3 **32.4**

NBS (1.48 g, 8.31 mmol) was added to a cooled (-15 °C, ice-salt) and stirred solution of dihydrofuran **32.3** (0.5287 g, 7.543 mmol) and **28.2** (1.99 g, 8.28 mmol) in THF (10 mL). The mixture was stirred for 2 h, and then stored at -5 °C overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.7 x 34 cm), using 15% EtOAc-hexane, gave **32.4** (2.12 g, 72%) as a foam: FTIR (CH_2Cl_2 cast) 1708, 1590, 1548, 1487, 1458 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.23-2.41 (m, 1 H), 2.61-2.81 (m, 1 H), 4.19-4.4 (m, 2 H), 4.42 (d, *J* = 5.4 Hz, 1 H), 6.43-6.57 (m, 2 H), 7.03-7.61 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) (several expected signals were not observed) δ 33.0 (t'), 44.9 (d'), 68.1 (t'), 96.2 (d'), 123.6 (d'), 130.5 (d'), 163.6 (s'); exact mass *m/z* calcd for $C_{18}H_{17}{}^{79}BrN_2O_3$ 388.0422, found 388.0422. The *trans* stereochemistry is assigned on the basis of mechanistic considerations and the value of the coupling constant for the OC**H**O proton (*J* = 5.4 Hz).

3-(2,2-Diphenylhydrazino)octahydro-2*H*-cyclohepta[b]furan-2-one (33.1).

32.2 **33.1**

The general procedure for radical cyclization was followed using **32.2** (590 mg, 1.42 mmol) in PhMe (90 mL),

Bu_3SnH (0.57 mL, 2.1 mmol) in PhMe (12 mL) and AIBN (22.9 mg, 0.139 mmol) in PhMe (12 mL). Flash chromatography of the crude product over silica gel (1.7 x 35 cm), using 15% EtOAc-hexane, gave **33.1** (268.9 mg, 56%) as a mixture of four isomers, of which only one could be separated from the others. Two fractions were obtained from the chromatography; one (235.2 mg) consisted of three isomers, and the other (33.7 mg) was a single isomer. The mixed fraction had: FTIR (CH_2Cl_2 cast) 1769 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.12-1.65 (m, 4.71 H), 1.65-2.16 (m, 4.74 H), 2.16-2.68 (m, 1 H), 2.86-3.0 (m, 0.19 H), 3.61-3.70 (m, 0.47 H), 4.03 (d, J = 7.8 Hz, 0.45 H), 4.12 (dt, J = 10.2, 4.3 Hz, 0.08 H), 4.5-4.64 (m, 0.89 H), 4.66-4.8 (m, 0.62 H), 4.92 (s, 0.14 H), 7.01-7.39 (m, 10 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 21.9 (t'), 22.2 (t'), 25.2 (t'), 25.6 (t'), 25.8 (t'), 27.1 (t'), 27.7 (t'), 28.8 (t'), 29.2 (t'), 30.3 (t'), 31.0 (t'), 31.2 (t'), 31.4 (t'), 31.5 (t'), 33.7 (t'), 45.7 (d'), 46.1 (d'), 50.8 (d'), 60.7 (d'), 62.1 (d'), 63.0 (d'), 81.4 (d'), 82.7 (d'), 83.8 (d'), 120.6 (d'), 120.7 (d'), 121.2 (d'), 123.0 (d'), 123.1 (d'), 123.5 (d'), 129.5 (d'), 129.6 (d'), 129.7 (d'), 147.4 (s'), 147.6 (s'), 148.0 (s'), 175.3 (s'), 175.4 (s'); exact mass calcd for $C_{21}H_{24}N_2O_2$ 336.1837, found 336.1832.

The single isomer had: FTIR (CH_2Cl_2 cast) 1777 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.48-1.95 (m, 9 H), 2.19-2.32 (m, 1 H); 2.34-2.47 (m, 1 H); 3.68 (dd, J = 6.3, 1.6 Hz, 1 H), 4.23 (d, J = 1.5 Hz, 1 H), 4.67 (dt, J = 10.1, 4.7 Hz, 1 H), 7.01-7.39 (m, 10 H), ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 23.7 (t'), 24.2

(t'), 26.0 (t'), 27.3 (t'), 33.4 (t'), 47.1 (d'), 59.4 (d'), 84.8 (d'), 121.0 (d'), 123.2 (d'), 129.6 (d'), 147.5 (s'), 174.5 (s'); exact mass *m/z* calcd for $C_{21}H_{24}N_2O_2$ 336.1837, found 336.1834.

The use of Ph_3SnH gave a similar yield. However, it was found that the separation of the crude mixture was easier than in the case of Bu_3SnH.

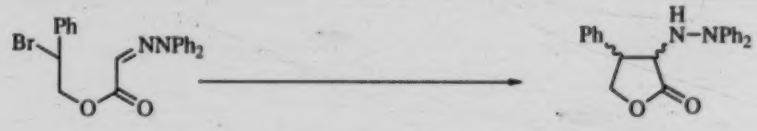
(3α,3aα,6aα)- and (3α,3aβ,6aβ)-3-(2,2-Diphenylhydrazino)tetrahydrofuro[2,3-b]furan-2(3*H*)-one (33.2).

32.4 **33.2**

The general procedure for radical cyclization was followed using **32.4** (753.4 mg, 1.942 mmol) in PhMe (120 mL), Bu_3SnH (847.8 mg, 2.913 mmol) in PhMe (15 mL) and AIBN (32.0 mg, 0.194 mmol) in PhMe (15 mL). Flash chromatography of the crude product over silica gel (1.7 x 34 cm), using 50% EtOAc-hexane, gave **33.2** (285.0 mg, 47%) as a colorless oil, which was a mixture [ca 1:1.4 (^{1}H NMR)] of two isomers: FTIR (CH_2Cl_2 cast) 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68-2.42 (m, 2 H), 3.18-3.30 (m, 1 H), 3.73-3.89 (m, 1 H), 4.0-4.18 (m, 2 H), 4.42-4.8 (br s, 1 H), 5.98 (d, *J* = 4.6 Hz, 0.53 H), 6.21 (d, *J* = 5.5 Hz, 0.37 H), 6.99-7.43 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.4 (t'), 30.3 (t'), 44.8 (d'), 45.0

(d'), 59.1 (d'), 62.4 (d'), 68.0 (t'), 69.4 (t'), 106.9 (d'), 108.2 (d'), 120.6 (d'), 120.8 (d'), 123.4 (d'), 129.5 (d'), 129.6 (d'), 146.9 (s'), 147.2 (s'), 173.0 (s'), 174.0 (s'); exact mass *m/z* calcd for $C_{18}H_{18}N_2O_3$ 310.1317, found 310.1309.

3-(2,2-Diphenylhydrazino)dihydro-4-phenyl-2(3*H*)-furanone (33.3).



32.6 **33.3**

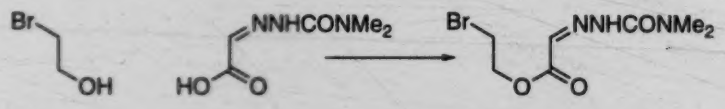
The general procedure for radical cyclization was followed, with the indicated modifications, using **32.6** (250.3 mg, 0.5931 mmol) in PhMe (37 mL), Bu_3SnH (0.24 mL, 0.89 mmol) in PhMe (5.25 mL), and AIBN (10.3 mg, 0.0627 mmol) in PhMe (5.25 mL). The residue was dissolved in Et_2O (50 mL) and the solution was agitated for 40 min in a sonicator [Branson, model B-12, 80 W] with an aqueous solution of KF (516 mg, 8.88 mmol) in water (10 mL).[39] The precipitate of Bu_3SnF was filtered off and the ethereal phase of the filtrate was separated. The aqueous layer was washed with Et_2O (3 x 50 mL) and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 10% EtOAc-hexane, gave the two individual isomers of **33.3** (117.5 mg and 55.5 mg, 85% in all) as yellow oils. The major (less polar) compound had: FTIR

(CH_2Cl_2 cast) 1732 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.88 (q, J = 9.4 Hz, 1 H), 4.18 (t, J = 9.6 Hz, 1 H), 4.12 (d, J = 9.6 Hz, 1 H), 4.70 (t, J = 9.0 Hz, 1 H), 4.83 (s, 1 H), 6.85-7.50 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 49.8 (d'), 62.3 (d'), 72.0 (t'), 120.6 (d'), 123.0 (d'), 127.9 (d'), 128.1 (d'), 129.1 (d'), 129.4 (d'), 137.5 (s'), 147.1 (s'), 175.1 (s'); exact mass m/z calcd for $C_{22}H_{20}N_2O_2$ 344.15247, found 344.15195.

The minor (more polar) isomer had: FTIR (CH_2Cl_2 cast) 1733 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.76-3.83 (m, 1 H), 4.16 (dd, J = 8.0, 1.5 Hz, 1 H), 4.35 (s, 1 H), 4.55-4.60 (m, 2 H), 6.85-7.45 (m, 15 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 45.9 (d'), 59.7 (d'), 72.4 (t'), 121.1 (d'), 123.3 (d'), 128.0 (d'), 128.7 (d'), 129.2 (d'), 129.4 (d'), 137.7 (s'), 147.5 (s'), 175.4 (s'); exact mass m/z calcd for $C_{22}H_{20}N_2O_2$ 344.15247, found 344.15187.

We did not assign the stereochemistry to the individual isomers, as the observed $J_{CHN\text{-}CHPh}$ values were comparable.

2-Bromoethyl [2-[(Dimethylamino)carbonyl]-hydrazono]acetate (35.2).

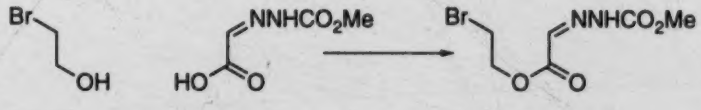


35.1 **34.2** **35.2**

The general procedure for coupling alcohols with **28.2**

was followed, using **34.2** (322 mg, 2.03 mmol), alcohol **35.1** (275 mg, 2.20 mmol), DCC (454 mg, 2.20 mmol), and DMAP (24 mg, 0.20 mmol) in THF (10 mL). After the usual overnight reaction period no starting material remained (TLC control, silica, 50% EtOAc-hexane). Flash chromatography of the crude product over silica gel (1.7 x 35 cm), using 80% EtOAc-CH_2Cl_2, gave **35.2** as a white solid. Recrystallization from EtOH-hexane gave **35.2** (0.381 g, 72%): mp 113-114 °C; FTIR (CH_2Cl_2 cast) 3224, 2934, 2856, 1749, 1717, 1592, 1547 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 3.0 (s, 6 H), 3.64 (t, J = 6.0 Hz, 2 H), 4.51 (t, J = 6.0 Hz, 2 H), 7.53 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) (two rotamers) δ 27.7 (t'), 28.0 (t'), 53.4 (q'), 53.5 (q'), 64.5 (t'), 64.6 (t'), 126.4 (d'), 134.0 (d'), 153.7 (s'), 161.1 (s'), 162.7 (s'); exact mass m/z calcd for $C_7H_{12}{}^{79}BrN_3O_3$ 265.0062, found 265.0069.

2-Bromoethyl [(Methoxycarbonyl)hydrazono]acetate (35.3).

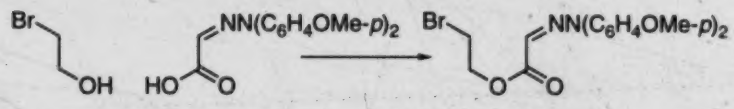


35.1 **34.4** **35.3**

The general procedure for coupling alcohols with **28.2** was followed, using **34.4** (307.2 mg, 2.103 mmol), alcohol **35.1** (288.7 mg, 2.311 mmol), DCC (476.6 mg, 2.311 mmol), and DMAP (25.7 mg, 0.211 mmol) in CH_2Cl_2 (10 mL). After the usual overnight reaction period no starting material remained (TLC

control, silica, 60% EtOAc-hexane). Flash chromatography of the crude product over silica gel (1.7 x 30 cm), using 60% EtOAc-hexane, gave a white solid. Recrystallization from $CHCl_3$-hexane gave **35.3** (402 mg, 76%) as a crystalline solid: mp 109-112 °C; FTIR (CH_2Cl_2 cast) 3223, 2934, 2855, 1750, 1719, 1592, 1548 cm^{-1}; ^1H NMR (CD_3OD containing a little D_2O) δ 3.66 (t, J = 5.9 Hz, 2 H), 3.83 (s, 3 H), 4.55 (t, J = 5.9 Hz, 2 H), 7.08 (s, 1 H); ^{13}C NMR (DMSO-d_6, 50.3 MHz) δ 30.4 (t'), 52.6 (q'), 64.3 (t'), 133.4 (d'), 153.5 (s'), 162.3 (s'); exact mass m/z calcd for $C_6H_9{}^{79}BrN_2O_4$ 251.9745, found 251.9746. An X-ray crystal structure was obtained.

Methoxyphenyl)hydrazono]acetate (35.4).

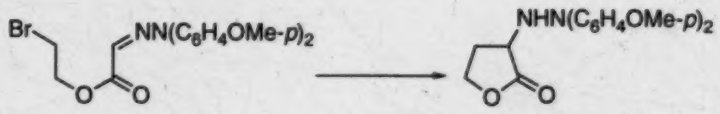


35.1 **34.3** **35.4**

The general procedure for coupling alcohols with **28.2** was followed, using **34.3** (2.321 g, 7.736 mmol), alcohol **35.1** (1.0384 g, 8.3092 mmol), DCC (1.7538 g, 8.4999 mol), and DMAP (0.0944 g, 0.773 mmol) in CH_2Cl_2 (15 mL). Flash chromatography of the crude product over silica gel (4 x 32 cm), using 10% EtOAc-hexane, gave **35.4** (2.7981 g, 89%) as a crystalline solid: mp 168-170 °C; FTIR (CH_2Cl_2 cast) 3001, 2954, 2835, 1726, 1701, 1604, 1584, 1548 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.58 (t, J = 6.1 Hz, 2 H), 3.82 (s, 6 H), 4.48 (t, J = 6.1 Hz, 2 H), 6.47 (s, 1 H), 6.89-7.17 (m, 8 H), ^{13}C NMR

(CD_2Cl_2, 50.3 MHz) δ 29.5 (t'), 55.8 (q'), 64.1 (t'), 115.4 (d'), 122.3 (d'), 158.3 (s'), 164.4 (s'); exact mass *m/z* calcd for $C_{18}H_{19}{}^{79}BrN_2O_4$ 406.0528, found 406.0524.

3-[2,2-Di(4-methoxyphenyl)hydrazino]dihydro-2(3*H*)-furanone (36.1).



35.4 **36.1**

The general procedure for radical cyclization was followed using **35.4** (230 mg, 0.566 mmol) in PhMe (35 mL), Bu_3SnH (247.4 mg, 0.8511 mmol) in PhMe (5 mL) and AIBN (9.30 mg, 0.057 mmol) in PhMe (5 mL). Flash chromatography of the crude product over silica gel (1.7 x 30 cm), using 20% EtOAc-hexane, gave **36.1** (133.1 mg, 71%) as a crystalline solid: mp 119-121 °C; FTIR (CH_2Cl_2 cast) 1772 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.25-2.40 (m, 1 H), 2.46-2.57 (m, 1 H), 3.73-3.86 (m, including a singlet at δ 3.75, 7 H in all), 4.21 (dt, J = 9.2, 6.7 Hz, 1 H), 4.37 (s, 1 H), 4.44 (dt, J = 8.7, 3.3 Hz, 1 H), 6.81-7.11 (m, 8 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 29.9 (t'), 55.8 (q' or d'); 56.0 (q' or d'), 66.8 (t'), 114.8 (d'), 122.3 (d'), 142.3 (s'), 156.1 (s'), 176.1 (s'); exact mass *m/z* calcd for $C_{18}H_{20}N_2O_4$ 328.1423, found 328.1422.

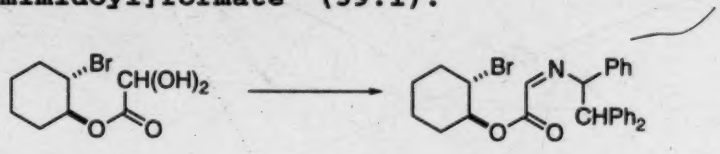
Dihydro-2,3-furandione 3-Di(4-methoxyphenyl)-

hydrazone (37.1).

36.1 **37.1**

DDQ (30.9 mg, 0.136 mmol) was added to a stirred solution of **36.1** (29.8 mg, 0.0908 mmol) in CH_2Cl_2 (2 mL) containing a small amount of water (0.15 mL. Reaction was complete within 5 min (TLC control, silica, 40% EtOAc-hexane). Saturated aqueous $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 10 mL). The organic extract was washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 40% EtOAc-hexane, gave **37.1** (0.0294 g, 99%) as a crystalline solid: mp 160-161 °C; FTIR (CH_2Cl_2 cast) 1759, 1505 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.09 (t, J = 7.3 Hz, 2 H), 3.81 (s, 6 H), 4.15 (t, J = 7.3 Hz, 2 H), 6.87-7.19 (m, 8 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 26.9 (t'), 55.9 (q'), 64.7 (t'), 114.6 (d'), 124.8 (d'), 127.9 (s'), 138.0 (s'), 158.2 (s'), 168.9 (s'); exact mass m/z calcd for $C_{18}H_{18}N_2O_4$ 326.1266, found 326.1275.

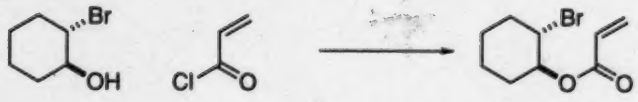
***Trans*-2-Bromocyclohexyl [*N*-(1,2,2-Triphenylethyl)formimidoyl]formate (39.1).**



41.3 **39.1**

A solution of amine **40.2**[40] (2.9326 g, 10.736 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of **41.3** (2.512 g, 10.73 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred overnight, and then evaporated. Flash chromatography of the residue over silica gel (4 x 32 cm), using 20% EtOAc-hexane, gave **39.1** (4.4311 g, 84%) as a foam: FTIR (CH_2Cl_2 cast) 1747, 1722 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.24-2.43 (m, 8 H), 3.96-4.15 (m, 1 H), 4.78 (dd, J = 10.3, 3.2 Hz, 1 H), 4.90-5.01 (m, 1 H), 5.51 (t, J = 11 Hz, 1 H), 7.04-7.53 (m, 16 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 23.6 (t'), 23.7 (t'), 25.8 (t'), 25.9 (t'), 31.3 (t'), 31.4 (t'), 36.0 (t'), 36.1 (t'), 52.8 (d'), 52.9 (d'), 58.3 (d'), 58.4 (d'), 77.4 (d'), 77.5 (d'), 79.7 (d'), 79.9 (d'), 126.8 (d'), 127.0 (d'), 127.1 (d'), 127.9 (d'), 128.4 (d'), 128.6 (d'), 128.7 (d'), 128.8 (d'), 128.90 (d'), 128.93 (d'), 129.1 (d'), 129.20 (d'), 129.24 (d'), 140.8 (s'), 140.9 (s'), 141.5 (s'), 141.6 (s'), 142.1 (s'), 153.4 (s'), 153.6 (s'), 161.6 (s'), 161.9 (s'); exact mass m/z calcd for $C_{28}H_{28}{}^{79}BrNO_2$ 489.1303, found 489.1309.

***Trans*-2-Bromocyclohexyl Propenoate (41.2).**



41.1 - **41.2**

Acryloyl chloride (987 mg, 10.9 mmol) was added slowly (over ca 10 min) to a stirred and cooled (0 °C) solution of *trans*-2-bromocyclohexanol **41.1**[41] (970 mg, 5.45 mmol), DMAP (18.3 mg, 0.818 mmol), and Et_3N (1.1029 g, 10.899 mmol) in CH_2Cl_2 (35 mL). Stirring at 0 °C was continued for 2 h, and then saturated aqueous $NaHCO_3$ (15 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 10% EtOAc-hexane, gave **41.2** (783.1 mg, 62%) as a colorless oil: FTIR (CH_2Cl_2 cast) 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.13-2.42 (m, 8 H), 3.88-4.07 (m, 1 H), 4.81-5.02 (m, 1 H), 5.76-5.88 (m, 1 H), 6.08 (ddd, J = 17.2, 10.3, 1.5 Hz, 1 H), 6.31-6.48 (m, 1 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.2 (t'), 25.4 (t'), 31.0 (t'), 35.5 (t'), 52.6 (d'), 75.8 (d'), 128.4 (d'), 131.0 (t'), 165.0 (s'); exact mass m/z calcd for $C_9H_{13}{}^{79}BrO_2$ 232.0098, found 232.0098.

Trans-2-Bromocyclohexyl Dihydroxyacetate (41.3).

41.2 **41.3**

OsO_4 (2.5% w/w in *t*-BuOH, 4.0 mg, 0.02 mmol) was added to a stirred mixture of acrylate **41.2** (457.3 mg, 1.971 mmol), water (2.7 mL) and dioxane (8 mL). After 10 min, the mixture had become dark brown. $NaIO_4$ (1.264 g, 5.909 mmol) was then added portionwise over ca 10 min, and the resulting mixture was stirred for 6 h. Brine (6.0 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and 10% aqueous $NaHSO_3$ (15 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 15% EtOAc-hexane, gave **41.3** (235.4 mg, ca 47%, assuming product is totally the dihydroxyacetate) as a colorless gum, which was used directly in the next step. The material was mainly the hydrate, but contained (^{1}H NMR) a small amount (ca 5 mol%) of the parent aldehyde (*trans*-2-bromocyclohexyl glyoxalate).

(3α,3aβ,7aβ)- and (3α,3aα,7aα)-3-aminohexahydro-2(3*H*)-benzofuranone Hydrochloride (41.4).

39.1 **41.4**

The general procedure for radical cyclization was followed using **39.1** (575.5 mg, 1.176 mmol) in PhMe (75 mL), Bu_3SnH (856.1 mg, 2.941 mmol) in PhMe (10 mL) and AIBN (20 mg, 0.12 mmol) in PhMe (10 mL). After evaporation of the solvent, hydrochloric acid (8 N, 10 mL) was added to the crude product and the solution was stirred for 1 h. The acidic solution was extracted with CH_2Cl_2 (2 x 20 mL) and the aqueous layer was evaporated under reduced pressure. In order to facilitate evaporation of HCl, EtOH (100%) was added periodically. After the evaporation, a yellow powder was obtained. This was dissolved in the minimum amount of EtOH, and Et_2O was then added until slight turbidity was observed. The mixture was kept at 5 °C overnight, to obtain **41.4**[30] as a white crystalline solid, which was recrystallized in the same way to give **41.4** (109.2 mg, 48%): mp 249-253 °C [(lit.[30b] 246 °C (decomp)]; FTIR (Microscope) 1775 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz) δ 0.98-1.93 (m, 7 H), 2.14 (d, J = 15.5 Hz, 1 H), 2.74-2.85 (m, 1 H), 4.48 (d, J = 6.5 Hz, 1 H), 4.68-4.77 (m, 1 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 20.4 (t'), 22.6 (t'), 23.3 (t'), 27.7 (t'), 39.1 (d'), 56.2 (d'), 78.2 (d'), 173.9 (s'); exact mass m/z calculated for $C_8H_{13}NO_2$ (M - HCl) 155.0946, found 155.0945. The *N*-acetate **42.1** was prepared[40] and had:

mp 170-174 °C (lit.[34b] 174-175 °C).

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Part 2

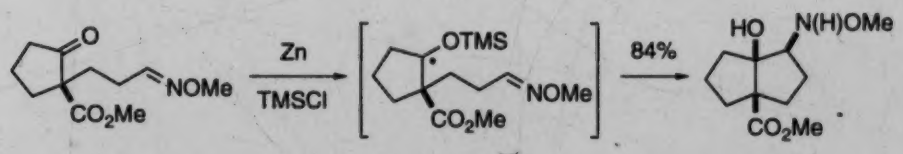
Radical Cyclization onto Oxime Ethers

I. Introduction

Oxime ethers were the first of the unsaturated nitrogen functional groups to be employed in radical reactions. The nucleophilic addition to the carbon-nitrogen double bond constitutes an extremely useful method for preparing a variety of amines.[1] Typically, organometallic reagents can be used to achieve such carbon-carbon bond-forming reactions. However, the mild addition of a neutral species, such as an uncharged free radical, would provide a highly general solution to the fundamental problems that are associated with the strong basicity of organometallic reagents. In this review both the inter- and intramolecular aspects of the radical reactions will be discussed.

A. Intramolecular Reactions

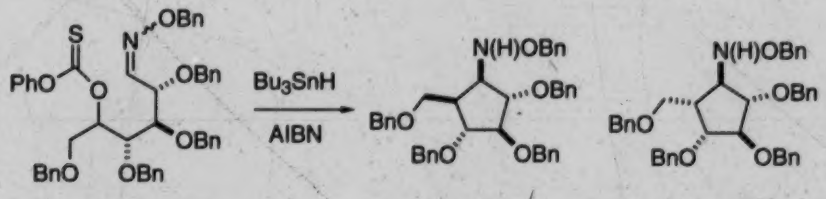
The first example of intramolecular radical addition onto oxime ether acceptors goes back to 1983. Corey and Pyne[2] generated the ketyl radical **1.2** by the treatment of a suitable cyclopentanone with zinc and chlorotrimethylsilane. The radical then cyclized to give **1.3** in 84% yield as a single diastereomer (Scheme 1).



1.1 **1.2** **1.3**

Scheme 1

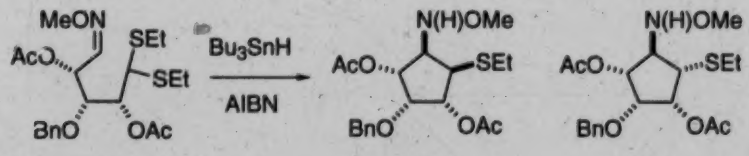
Bartlett *et al.*[3] have used *O*-benzyloxime acceptors for the synthesis of polysubstituted cyclopentanes and cyclohexanes from both bromide and phenylthiocarbonate precursors. D-Glucose was transformed into *O*-benzyloxime **2.1** and then radical cyclization of **2.1** afforded **2.2** and **2.3** in a 62:38 ratio and in 93% combined yield (Scheme 2).



2.1 **2.2** **2.3**

Scheme 2

A derivative of the sugar hydrolase inhibitor mannostatin A was synthesized by Moore and coworkers,[4] starting from a sugar derivative. Treatment of **3.1** with tributyltin hydride in the presence of AIBN afforded **3.2** and **3.3** in 80% yield and in a ratio of 3:1 (Scheme 3).

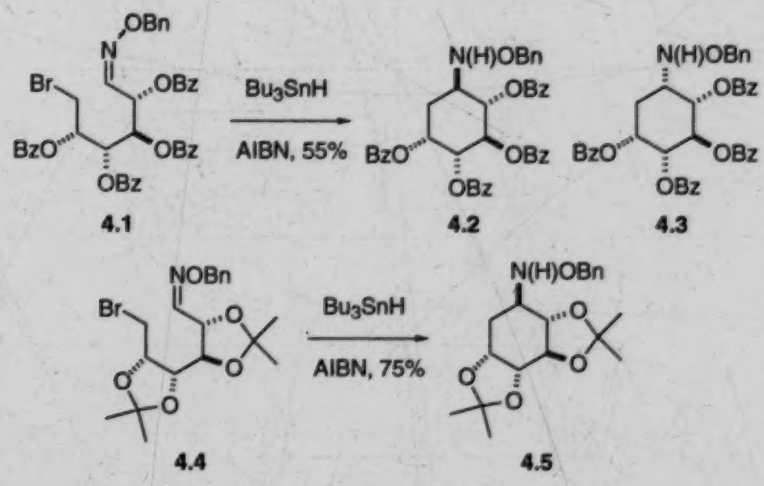


3.1 **3.2** **3.3**

Scheme 3

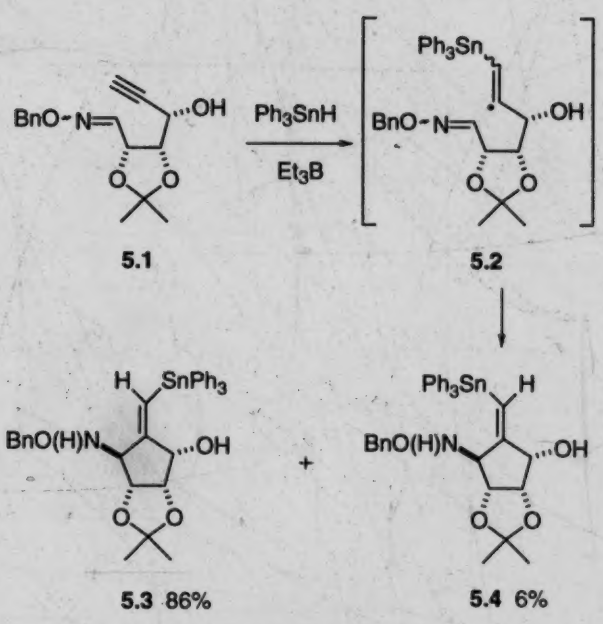
Marco-Contelles and coworkers have made extensive studies of radical cyclization reactions on sugar-based

oximes. They have reported[5] the 6-*exo* cyclizations of the acyclic carbohydrate-derived *O*-benzyloxime **4.1** (Scheme 4). Cyclization afforded a 3:1 mixture of **4.2** and **4.3** in 55% yield. They have found that the stereoselectivity was improved significantly when the number of conformers is reduced by the presence of isopropylidene acetals. Thus, the oxime ether **4.4** in the *gluco* series cyclized in 75% yield to the carbocycle **4.5** with a diastereomeric excess of 82%.



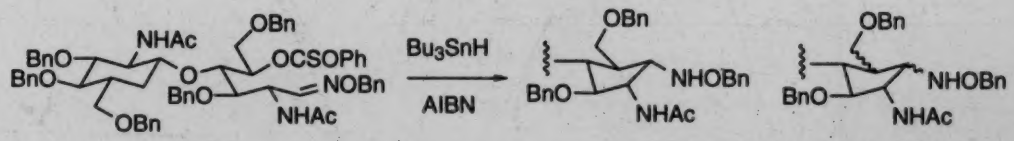
Scheme 4

Marco-Contelles[6] has also studied the cyclization reactions of vinyl radicals on carbohydrate substrates. When alkyne **5.1** was treated with triphenyltin hydride in the presence of triethylborane it initially afforded the intermediate vinyl radical **5.2**; the 5-*exo* closure of this radical onto the oxime ether then resulted in cyclopentanols **5.3** and **5.4** in an 86:6 ratio of the *Z* and *E* isomers (Scheme 5).



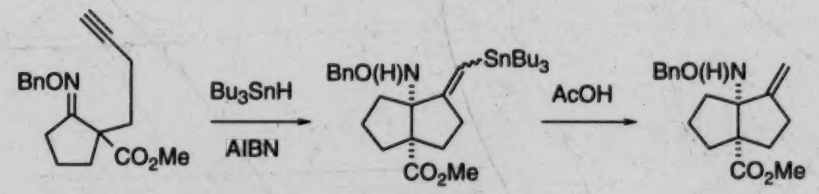
Scheme 5

An extension of this carbohydrate carbocyclization strategy to a disaccharide has been reported by Takahashi *et al.*[7] Comparison of the stereoselectivity at various temperatures was studied. Optimal results were obtained using AIBN in refluxing toluene, giving 31% of **6.2**, which was used to prepare a truncated disaccharide analog of the chitinase inhibitor allosamidin (Scheme 6).



Scheme 6

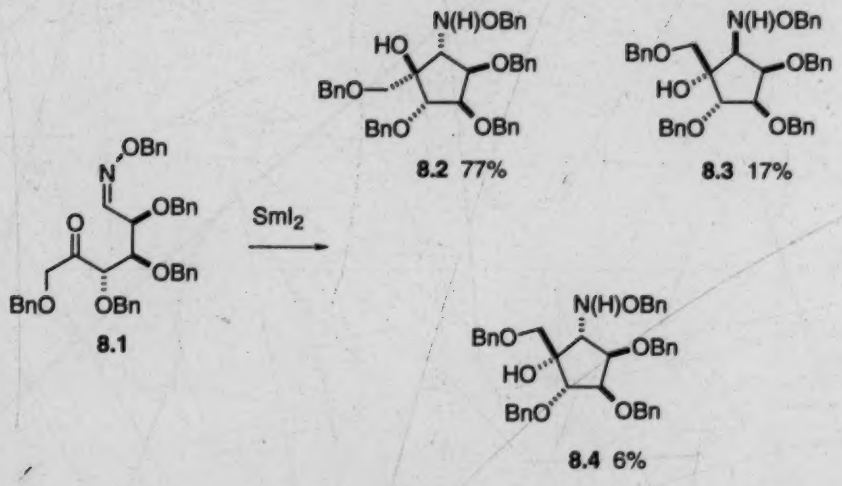
Enholm and coworkers[8] have also reported the cyclization of vinyl radicals onto oxime ethers. When compound **7.1**, for example was treated with tributyltin hydride in the presence of AIBN, compound **7.2** was isolated (Scheme 7). Protodestannylation with acetic acid afforded cyclopentanes **7.3**. Several cases were studied, each giving an olefinic hydroxylamine and the yield ranged from 56% to 90%.



7.1 **7.2** **7.3**

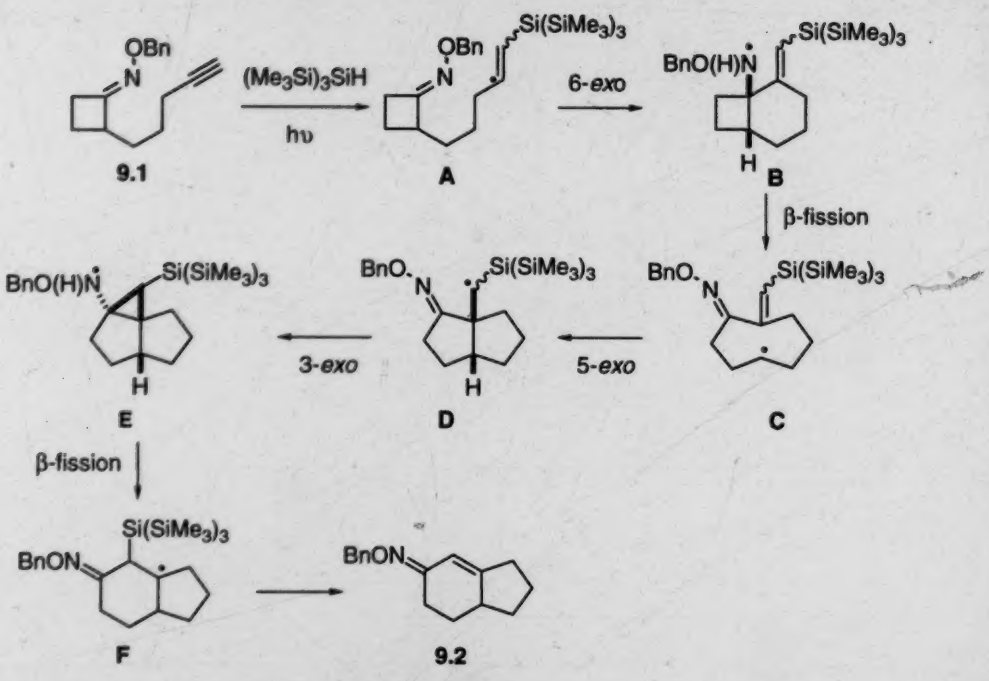
Scheme 7

Marco-Contelles[9] has investigated SmI_2-promoted cyclizations onto oxime ethers. When **8.1**, derived from D-mannose, was treated with SmI_2, it afforded a mixture of three aminocyclopentitols **8.2**, **8.3**, and **8.4** in a 13:3:1 ratio (Scheme 8).



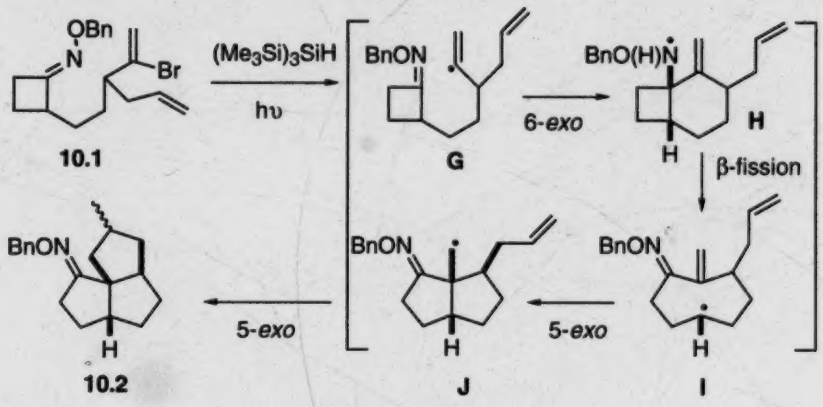
Scheme 8

A very interesting radical cascade sequence for the synthesis of bi- and tricyclic ring systems and involving the oxime ether acceptors has been reported by Pattenden *et al.*[10] When cyclobutanone oxime **9.1** was irradiated (Scheme 9) in the presence of tris(trimethylsilyl)silane, a vinyl tris(trimethylsilyl)silyl radical **A** was formed. This then underwent 6-*exo* cyclization onto the oxime ether to give intermediate radical **B**. β-Fission of this new radical led, sequentially to the intermediates **C** and **D**. The latter underwent another cyclization onto the oxime, resulting in a cyclopropane system. A second β-fission afforded **F**, and, finally, elimination of the tris(trimethylsilyl)silyl radical gave **9.2**, the silyl radical released serving to continue the chain.



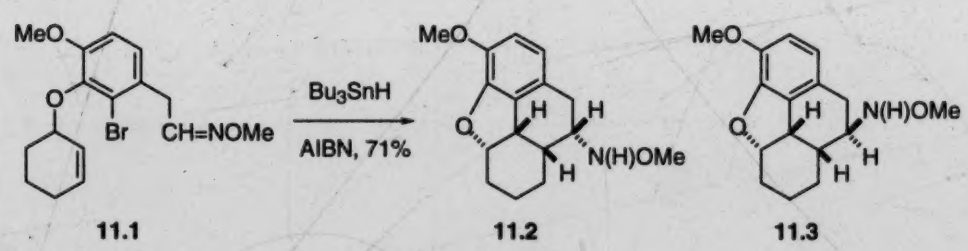
Scheme 9

Subsequent studies by Pattenden and coworkers[11] with an appropriate allyl side chain attached to the starting material then permitted an additional cyclization so as to generate a triquinane system (Scheme 10). Thus, irradiation of **10.1** in the presence of tris(trimethylsilyl)silane resulted in triquinane **10.2** as a 1:1 mixture of α- and β-methyl diastereomers in 38% yield. The product was a result a radical cascade involving a 6-*exo* cyclization (**G→H**), aminyl radical fragmentation (**H→I**), 5-*exo* radical transannulation (**I→J**), and, finally, a further 5-*exo* ring closure to the tricyclic system.



Scheme 10

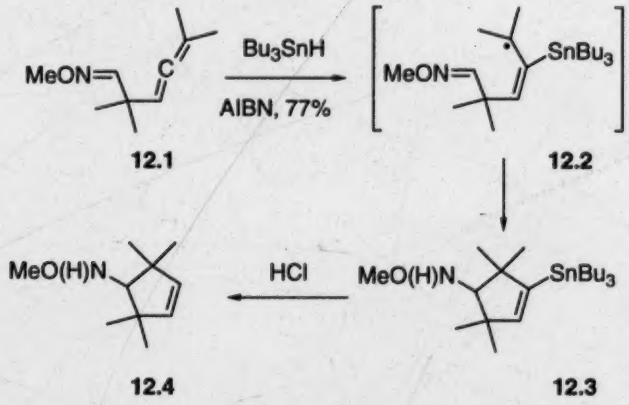
Another example of tandem cyclization onto oxime ethers was reported by Parker and coworkers.[12] They employed the oxime ether **11.1**, the cyclization of which ultimately leads to a morphine-like skeleton (Scheme 11). In this case, 5-*exo* cyclization onto the cyclohexene double bond, followed by 6-*exo* closure onto the oxime, generated isomeric compounds **11.2** and **11.3** in a ratio of 56:44 (71% yield).



Scheme 11

Hatem and coworkers[13] have synthesized cyclopentenes by radical cyclization of β-allenic *O*-methyloximes (Scheme 12). For example, when **12.1** was treated with tributyltin hydride

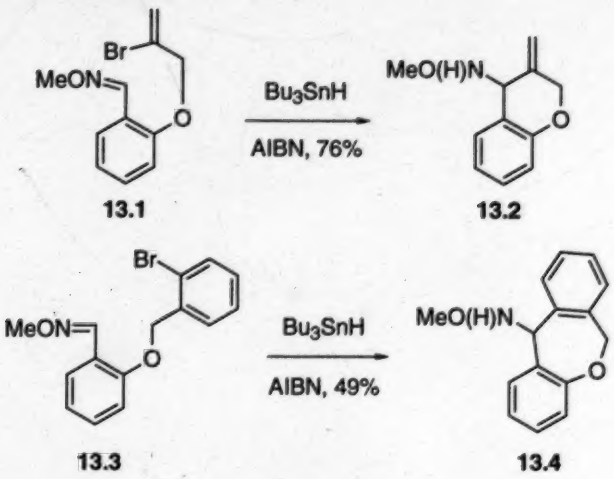
in the presence of AIBN, cyclopentene **12.3** bearing a protected hydroxylamine group and a vinyl stannyl functionality was isolated in 77% yield. Protodestannylation then gave the final cyclopentene **12.4**.



12.1 **12.2** **12.4** **12.3**

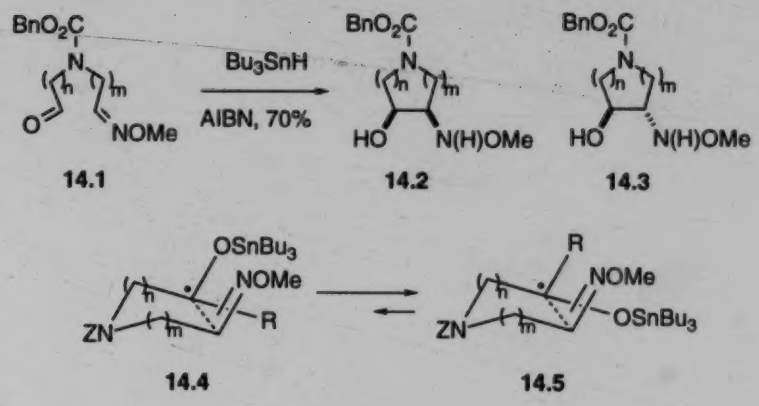
Scheme 12

Jenkins and coworkers[14] have made six- and seven-membered cyclic ethers by closure onto oxime ethers (Scheme 13). Treatment of bromide **13.1** with tributyltin hydride gave the heterocyclic olefin **13.2** in 76% yield. An oxacycloheptane **13.4** was made similarly in 49% yield.



Scheme 13

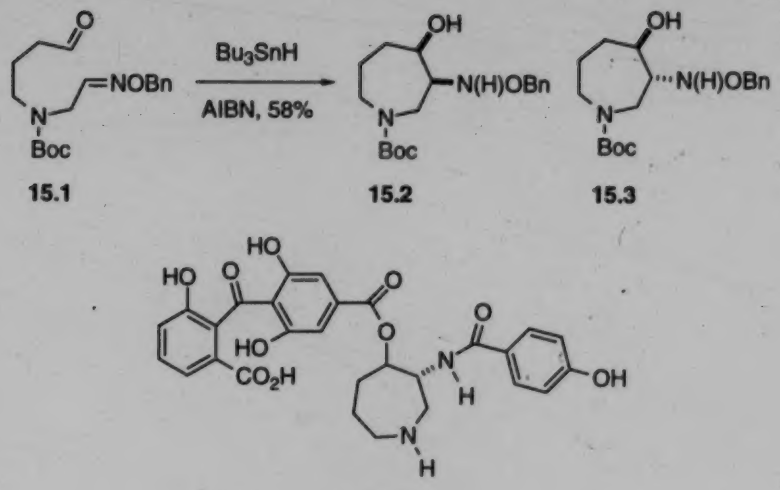
Five-, six-, and seven-membered nitrogen heterocycles are also accessible by cyclization onto oxime ether acceptors (Scheme 14).[15] Using such an approach, cyclic α-amino alcohols **14.2** and **14.3** were formed from the ketyl radical generated upon treatment of aldehyde oxime ethers **14.1** with tributyltin hydride. Ketones, bearing a distal oxime ether functionality underwent comparable cyclizations. For both aldehydes and ketones the *trans* isomer was predominant in all the cases and the best yield reported was 71% for **14.1**, n = 2, m = 1. The stereochemical outcome is explained by transition state models **14.4** and **14.5** (Scheme 14), where steric and electronic repulsions in **14.4** are larger than in **14.5**.



14.1 **14.2** **14.3** **14.4** **14.5**

Scheme 14

Using this type of reaction, Naito[16] has synthesized a substructure of (-)-balanol (Scheme 15), which is a natural product known to be a potent inhibitor of protein kinase C enzymes. The hexahydroazepine ring in this natural product contains adjacent amino alcohol groups in a *trans* relationship, which is the predominant isomer in the above examples. Cyclization of **15.1** gave **15.2** and **15.3** in a ratio of 2:3 (58% yield). The major isomer was resolved for subsequent conversion to (-)-balanol.

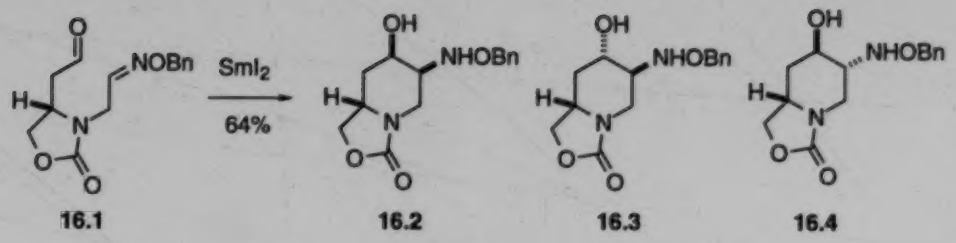


15.1 15.2 15.3

(-)-balanol

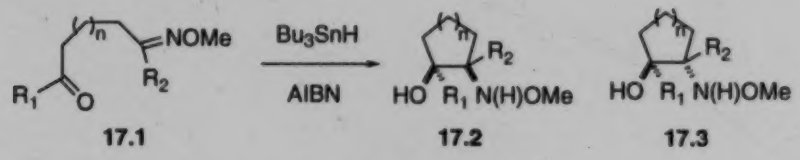
Scheme 15

As is well-known, the use of pre-existing chirality in a molecule allows access to enantiomerically pure products. Naito and coworkers[17] have employed L-aspartic acid as a precursor to prepare the cyclization substrate **16.1**, wherein the two reactive centers are tethered by an optically pure oxazolidinone (Scheme 16). Cyclization via the samarium ketyl afforded mixtures of three diastereomers in variable ratios, depending on temperature and additives. The separated diastereomers were further transformed (not shown) into protected hydroxymethyl piperidines that are potentially useful for the synthesis of diastereomeric pseudodistomin natural products – a compound class that has potent *in vitro* antineoplastic activity against certain leukemia cells.



Scheme 16

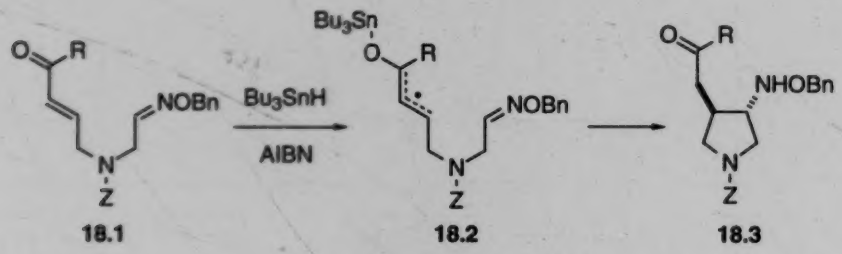
Fu[18] has reported that aldehyde or ketone oxime ethers bearing a suitably located ketone carbonyl, such as **17.1** (n = 1-2; R_1, R_2 = H or Me), in the presence of tributyltin hydride and AIBN give alcohols **17.2** and **17.3**, in which there is a 1,2-relationship between the hydroxy and nitrogen substituents. The *trans* isomer predominates in this cyclization (Scheme 17).



Scheme 17

In related cyclizations of α,β-unsaturated carbonyl systems such as **18.1**, the *trans* product was exclusively formed in the 5-*exo* cyclization (Scheme 18). Equilibration via reversible cyclization of a stabilized allylic *O*-stannyl ketyl radical was proposed to account for the selectivity in favor of the more stable *trans*-disubstituted pyrrolidine ring.[19] However, when the vinylogous relationship was applied to the oxime acceptor instead (not shown), a nearly 1:1

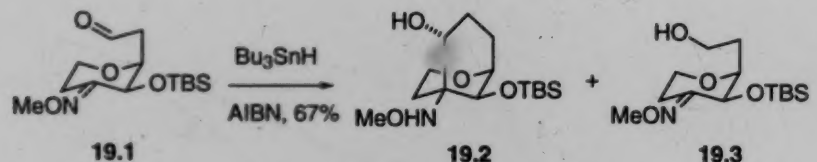
mixture of *cis/trans* products was obtained via ketyl or vinylogous ketyl addition to the C=C bond of the unsaturated oxime ether.



18.1 18.2 18.3

Scheme 18

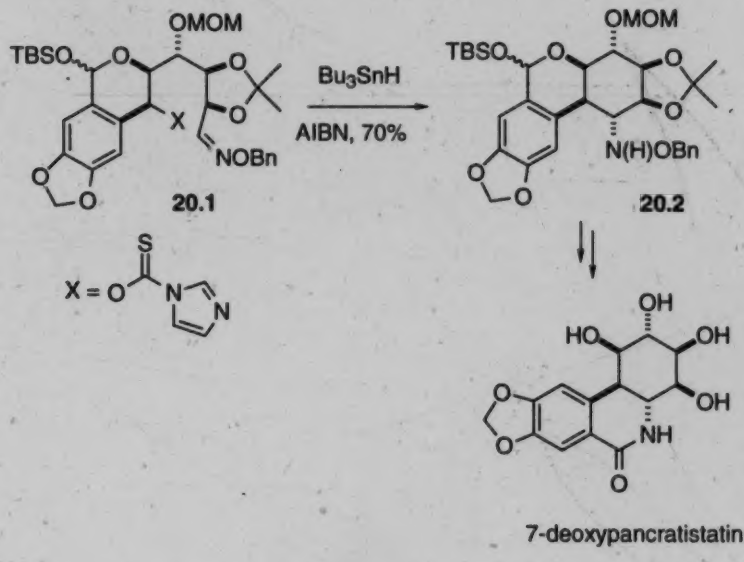
In the preparation of constrained bicyclic amino alcohols for use in the synthesis of oligonucleotide analogs, Leumann[20] tested various conditions for ketyl cyclization of an oxime ether for the key C-C bond construction (Scheme 19). Neither Ti(III) nor Zn/Me_3SiCl were successful, but treatment with Bu_3SnH and AIBN in toluene gave a moderate yield of the bicyclic product **19.2** along with the uncyclized reduction product **19.3**. High diastereoselectivity in the formation of **19.2** was attributed to steric direction by the proximal siloxy substituent, which ensures that the oxygen of the intermediate ketyl radical is directed away from the bulky siloxy group.



19.1 19.2 19.3

Scheme 19

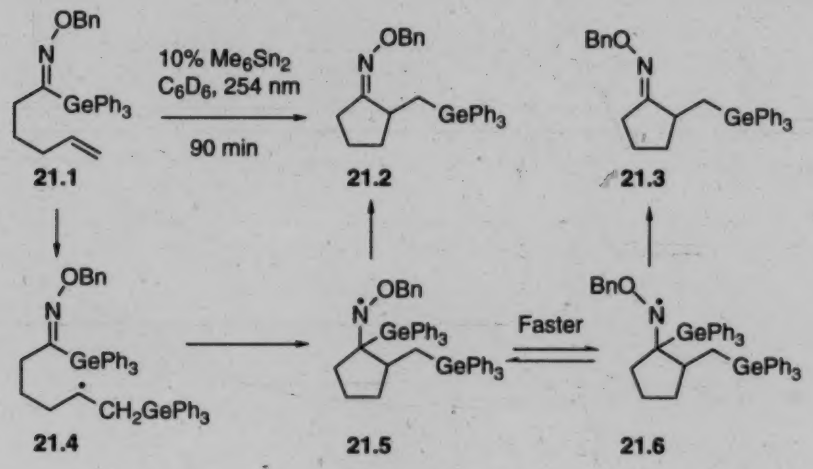
In their total synthesis of alkaloid 7-deoxypancratistatin, Keck and coworkers[21] used radical cyclization onto an oxime ether (Scheme 20). When compound **20.1** was subjected to radical conditions it cyclized to give compound **20.2** in 70% yield, and subsequent elaboration of this intermediate gave 7-deoxypancratistatin. The stereochemical preference of the nitrogen substituent in **20.2** has been explained in the terms given in Part 1 of this Thesis, Scheme 19.



Scheme 20

Curran[22] has reported a synthesis of cyclic oxime ethers by radical cyclization of acylgermane oxime ethers. Thus, when **21.1** was irradiated in benzene in the presence of hexamethylditin for 90 minutes, products **21.2** and **21.3** were

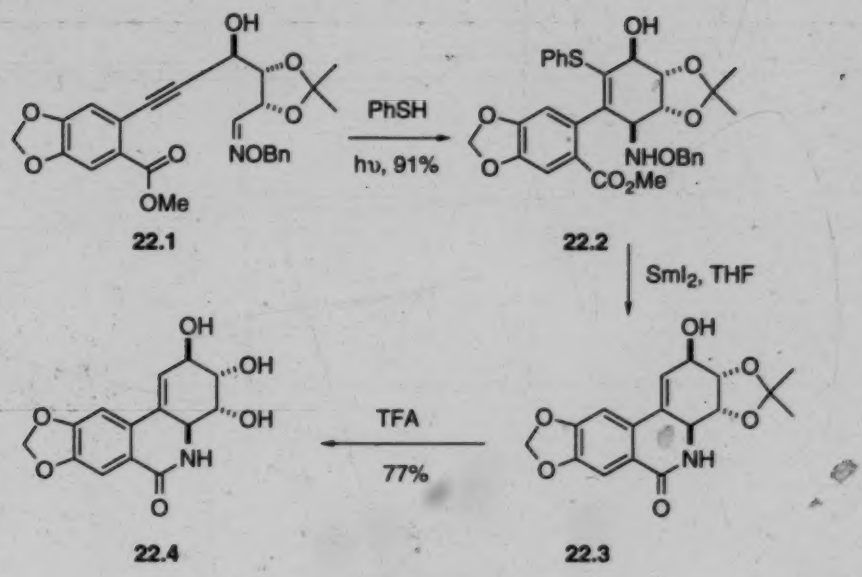
isolated in a ratio of 6.7:1 (Scheme 21), and the major isomer was isolated in 64% yield. It was suggested that the major (*trans*) isomer resulted from inversion of the substrate during the reaction. This suggests that bond rotation of the intermediate radical **21.5**, to give **21.6**, is faster than elimination of the triphenylgermyl radical, leading to **21.2**.



Scheme 21

The first total synthesis of (-)-lycoricidine and related natural products by radical method was achieved[23] by radical cyclization onto an oxime ether moiety (Scheme 22). Thus, reaction of hydroxy ester **22.1** with thiophenol in toluene solution, under irradiation from a sunlamp, afforded the cyclized product **22.2** as a single isomer in 91% yield. Subjection of **22.2** to treatment with SmI_2[24] effected three operations: reductive cleavage of the N-O bond, cyclization of the resulting amino ester, and removal of the phenylthio group, affording **22.3** in 76% yield. Removal of the acetonide

moiety then gave the final product.

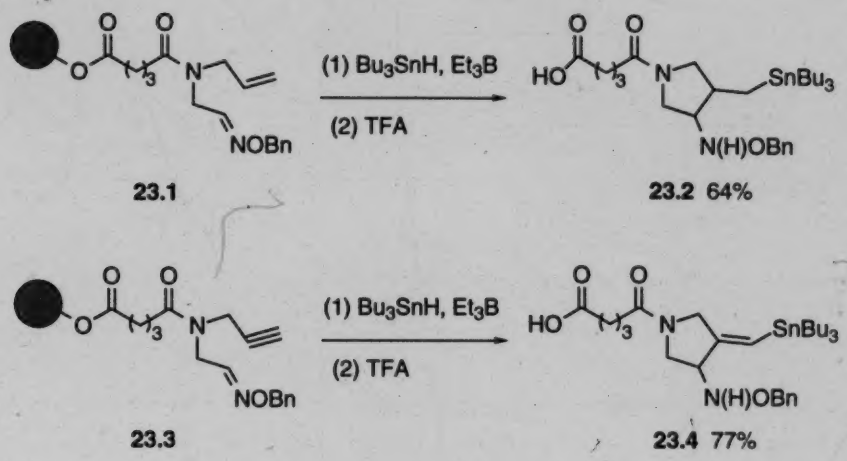


22.1 22.2 22.3 22.4

Scheme 22

The radical chemistry of oxime ethers has been extended to the solid phase. Naito *et al.*[25] have found that radical cyclization of oxime ethers anchored to a polymer support proceeded smoothly by the use of triethylborane as a radical initiator. In the examples studied, the reactions provide functionalized pyrrolidines (Scheme 23). The yield for the reactions in solid phase were found to be lower than in solution phase. However, the tedious workup to remove tin residues from the reaction mixture is eliminated by simply washing the resin with solvents before detaching the product from the support. In a typical example, cyclization of **23.1** in the presence of Bu_3SnH with initiation by Et_3B and air, followed by the cleavage from the resin gave 64% yield of

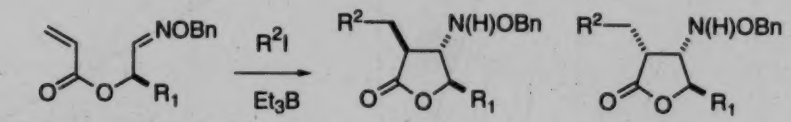
23.2. Under similar conditions **23.3** resulted in **23.4** in 77% yield.



Scheme 23

The same laboratory has reported[26] the radical addition-cyclization reaction (Scheme 24) of substrates having two different radical acceptors, one of them being an oxime ether. Cyclization of **24.1** under different radical conditions gave a mixture of **24.2** and **24.3** (Scheme 24). The best yield (80%) was obtained when R_2 = *i*-Pr and when the reaction was done in 1:4 water-methanol as solvent at reflux. The best diastereoselectivity (18:1) was obtained when R_2 = Et and toluene was used as a solvent at room temperature (53% yield). Increasing the reaction temperature tended to decrease the diastereoselectivity. However, the increase in temperature was found to increase the yield due to higher population of the reactive conformer of the ester moiety. When substrate **24.4** (R_1 = H) was treated to similar

conditions, the reaction proceeded in a slightly low yield and with a very low diastereoselectivity. Clearly, the bulky substituent R_1 at the chiral center was important not only for selectivity but also for efficient cyclization.



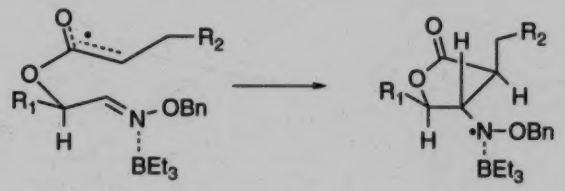
24.1 R_1 = TBDPSOCH$_2$
24.4 R_1 = H

24.2 Major

24.3 Minor

Scheme 24

The diastereoselectivity observed in these reactions has been explained as summarized in Scheme 25. Non-bonded interactions are judged to be minimized in conformer **25.1** which leads to the observed major product.

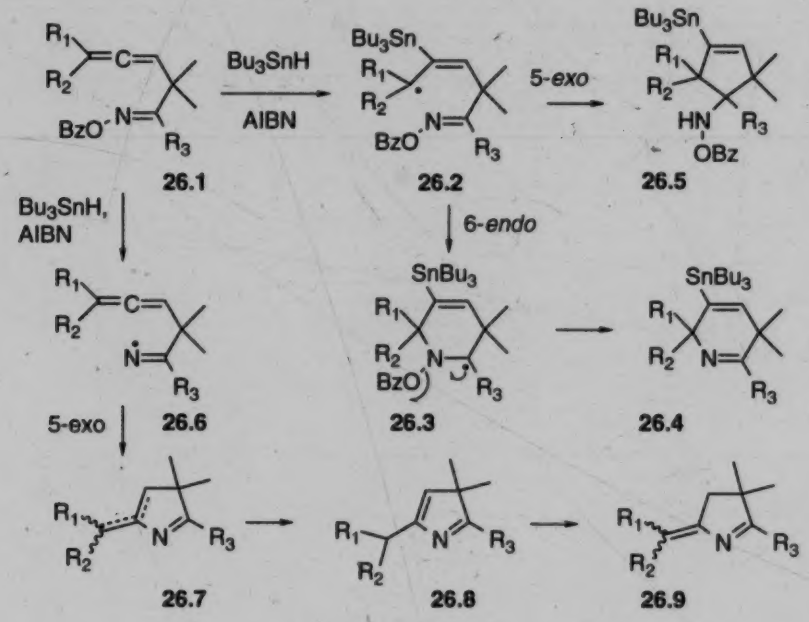


25.1 **25.2**

Scheme 25

Hatem and coworkers[27] have investigated radical cyclizations with a series of *O*-benzoyloximes **26.1** incorporating an allene unit (Scheme 26). Depending on the substitution pattern, a wide range of compounds has been obtained. If the stannyl radical adds to the allene segment of **26.1**, the resulting carbon-centered radical undergoes

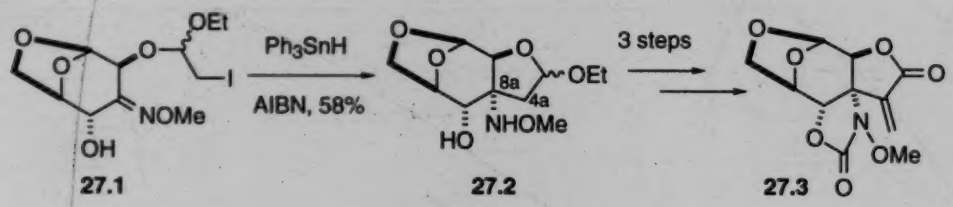
either a 5-*exo* ring closure to give the cyclopentene derivatives **26.5** or a 6-*endo* ring closure onto the N atom to give the dihydropyridines **26.4**. If the stannyl radical adds to the benzoyl group instead, an iminyl radical is formed, which gives the 3*H*-pyrroles **26.8** and the alkylidene pyrrolines **26.9**. The course of the reaction appears to be governed by subtle steric as well as polar effects.



Scheme 26

The considerable synthetic challenge posed by tetrodotoxin has prompted the development of radical cyclization approaches to construct its C(8a) amine-bearing stereogenic center. Alonso and coworkers[28] have done extensive studies on the use of radical cyclizations in this field. When compound **27.1** was subjected to radical

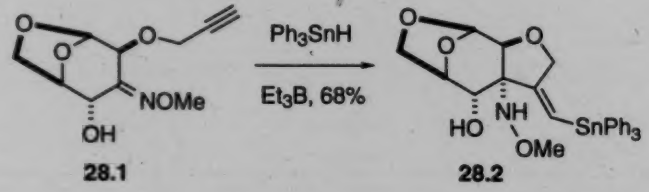
cyclization conditions, using triphenyltin hydride and AIBN, compound **27.2** was formed with complete diastereoselectivity, thereby constructing the C(8a)-C(4a) bond of the tetrodotoxin skeleton (Scheme 27). Further manipulation of this compound converted the acetal to the *exo*-methylene lactone **27.3** in three steps. Compound **27.3** is regarded as a potential key intermediate for the total synthesis of tetrodotoxin.



27.1 **27.2** **27.3**

Scheme 27

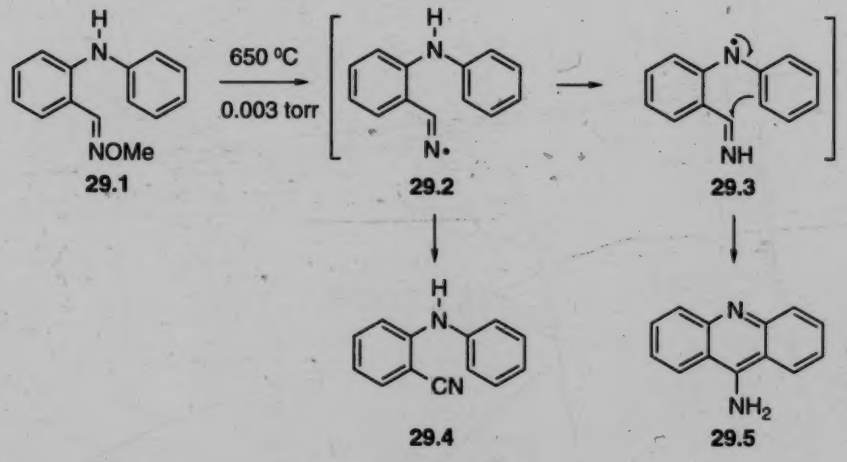
Alonso *et al.*[28] have also examined stannyl addition-cyclization during their tetrodotoxin synthetic work. When alkyne **28.1** was treated with triphenyltin hydride in the presence of triethylborane a cyclized vinylstannane (**28.2**) was obtained in 68% yield (Scheme 28). However, subsequent transformations toward tetrodotoxin were best achieved using the haloacetal radical cyclization product described above (Scheme 27).



28.1 **28.2**

Scheme 28

McNab and coworkers[29] have reported that flash vacuum pyrolysis of oxime ethers gives iminyl radicals which undergo various secondary processes, including addition to a C=N bond (Scheme 29). Formation of **29.5** from aldoxime **29.1** was attributed to tandem reactions involving N-O homolysis, radical translocation, and 6-*exo* cyclization onto the C=N bond. The related acetophenone ketoxime (not shown) gave a complex mixture of products.

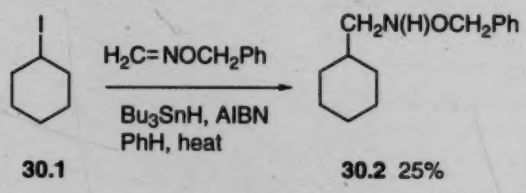


Scheme 29

B. Intermolecular Reactions

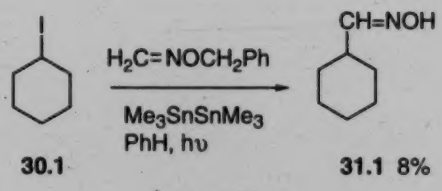
The intermolecular addition of carbon radicals to oxime ethers has received much less attention compared to the intramolecular versions. Hart's group[30] reported the first such studies and they examined the intermolecular alkyl radical addition to *O*-benzylformaldoxime. Treatment of excess of formaldoxime with Bu_3SnH and AIBN in the presence of one equivalent of iodocyclohexane (**30.1**) gave only 25%

yield of the desired product **30.2** (Scheme 30).



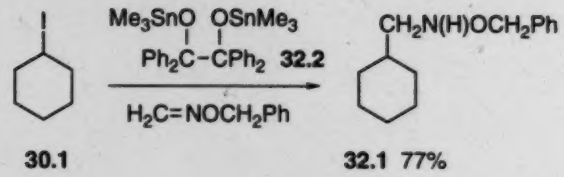
Scheme 30

Irradiation of a benzene solution of iodocyclohexane (**30.1**) and benzylformaldoxime in the presence of 1.2 equivalents of hexamethylditin gave cyclohexane carboxaldoxime **31.1**, in only 8% yield (Scheme 31). This product may have been generated by the addition of a cyclohexyl radical to *O*-benzylformaldoxime followed by fragmentation and tautomerization of the resulting nitroso compound.



Scheme 31

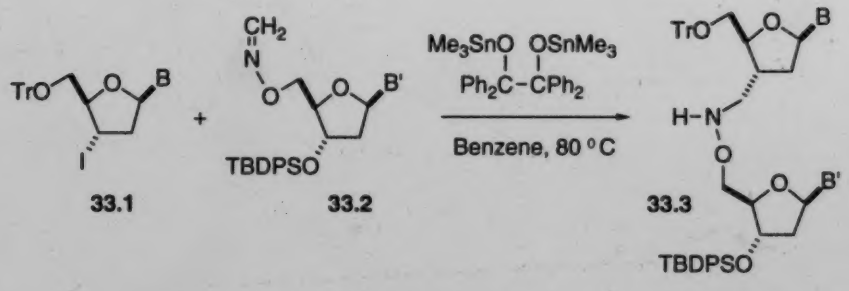
However, when the radical reaction was done in the presence of bis(trimethylstannyl)benzopinacolate (**32.2**) as a source of stannyl radicals, using hot (60 °C) benzene, they obtained 77% of the desired product **32.1** (Scheme 32).



30.1 32.1 77%

Scheme 32

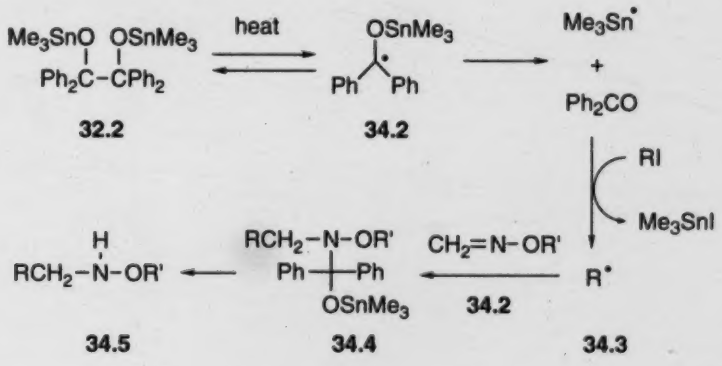
Use of bis(trimethylstannyl)benzopinacolate in intermolecular radical reaction of oxime ethers has also been reported by Bhat *et al.*[31] They have employed this method to prepare a series of dimeric nucleosides as mimics of natural nucleic acids (Scheme 33). In one example, the reaction of iodide **33.1** with oxime **33.2** in the presence of bis(trimethylstannyl)benzopinacolate in degassed benzene gave an 81% yield of **33.3**.



Scheme 33

Hart[30] has suggested that these radical reactions might involve a free radical non-chain processes. Thus, bis(trimethylstannyl)benzopinacolate **32.2** is decomposed thermally to provide the (presumably) stabilized stannyl ketyl radical **34.2**, which then can decompose to afford benzophenone and a trimethylstannyl radical (Scheme 34).

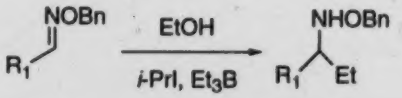
Alkyl iodides react with stannyl radicals extremely rapidly and irreversibly to give the tin iodide, and an alkyl radical **34.3**, which can then be trapped, in this case by an oxime, to provide a presumed *N*-centered radical species (not shown). It has been proposed by Hart that this radical then combines with the stabilized radical **34.2**, which is then hydrolyzed to the observed product **34.5**.



Scheme 34

Naito and coworkers[32] have reported the use of Lewis acids in intermolecular radical additions to oximes. Intermolecular addition of an ethyl radical, generated from a large excess of ethyl iodide (5 equiv.) and Et_3B (2.5 equiv.) as radical initiator, to either the formaldoxime ether **35.1** or the sterically more hindered glyoxylic oxime ether **35.2** which is, however, activated by an electron-withdrawing substituent, proceeded smoothly to give an excellent yield of ethylated product **35.4** and **35.5**, respectively (Scheme 35). However, the unactivated aldoxime ether **35.3** did not react at all under the same conditions. However, when the reaction

was carried out in the presence of a twofold excess of $BF_3.OEt_2$, the unactivated aldoxime ether **35.3** gave 95% of the desired product.

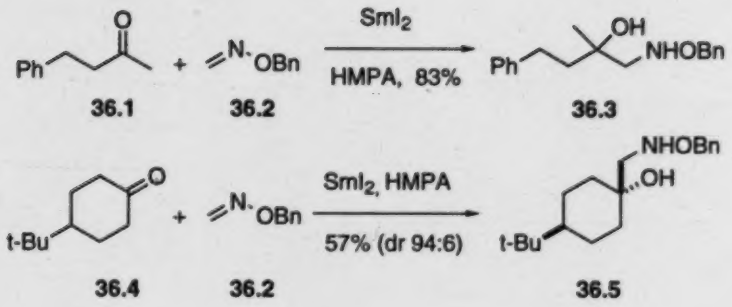


35.1 $R_1 = H$ **35.4** $R_1 = H$
35.2 $R_1 = CO_2Me$ **35.5** $R_1 = CO_2Me$
35.3 $R_1 = Et$ **35.6** $R_1 = Et$

Scheme 35

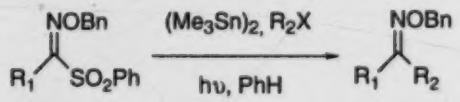
The effect of various Lewis acids on this reaction was investigated, and a two-fold excess of $BF_3.OEt_2$ was found to be the optimum.

Inanaga[33] has reported the use of *O*-benzyl formaldoxime in intermolecular samarium-mediated pinacol type addition reactions (Scheme 36). Representative examples are the (alkoxyamino)methylation of 4-phenyl-2-butanone (**36.1**) to provide alcohol **36.3** in high yield, and of 4-*t*-butyl-cyclohexanone (**36.4**) to afford the axial (alkoxyamino)methyl alcohol **36.5**. Several other difunctional 1,2-(alkoxyamino) alcohols were formed in moderate yield.



Scheme 36

Kim and coworkers[34] have developed an intermolecular radical reaction which retains the oxime ether functionality. For this purpose, radical fragmentation of a bond to the carbon terminus of the C=N bond, as in phenylsulfonyl oxime ether **37.1**, was used (Scheme 37). Irradiation of a wide variety of simple and functionalized alkyl iodides (1 equiv.) in the presence of oxime ethers **37.1** or **37.2** (2 equiv.) and hexamethylditin (1.2 equiv.) led to the addition-elimination products **37.3** in good yield.



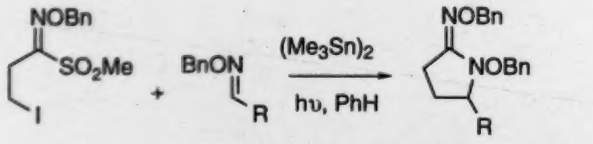
37.1 R_1 = H
37.2 R_1 = Me

37.3

Scheme 37

Kim[35] has also reported a tandem sequence involving an intermolecular addition to *O*-benzylformaldoxime or acetaldoxime, followed by cyclization of the resulting aminyl radical onto a *C*-sulfonyloxime ether, providing iminolactam

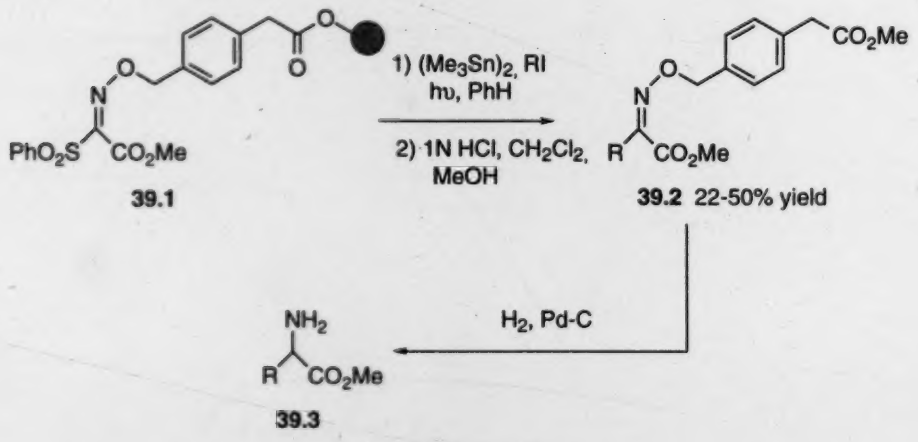
heterocycles in reasonable yields (Scheme 38).



38.1 **38.2** R = H **38.3** R = Me **38.4** R = H, 56% **38.5** R = Me, 53%

Scheme 38

The radical addition reactions of these *C*-sulfonyl oxime ethers has also been done on a solid support by Kim and coworkers.[36] Using a solid phase, and attachment through a modified *O*-benzyl group on the oxime, a series of radical additions of alkyl halides to the resin-linked acceptor gave the corresponding *C*-alkylated oxime ethers **39.2**, after detachment from the resin (Scheme 39). Hydrogenation of these products then led to the α-amino esters **39.3**.

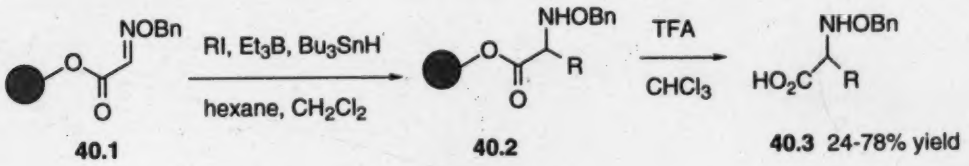


39.1 **39.2** 22-50% yield **39.3**

Scheme 39

Solid supports have also been used in intermolecular

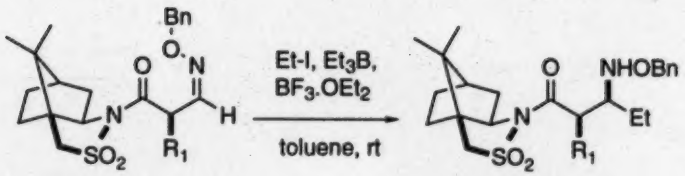
radical reactions of glyoxylic oxime ethers.[37] The radical acceptor was attached to the resin through the carboxylate group (Scheme 40), and the addition of several alkyl groups gave the corresponding hydroxyamino acids **40.3** after cleavage from the resin.



40.1 **40.2** **40.3** 24-78% yield

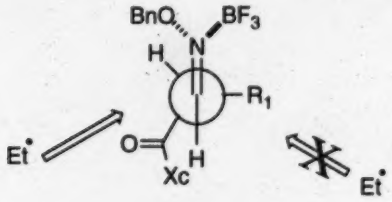
Scheme 40

Some examples of the effects of a neighboring chiral center on the addition to C=N bonds of oxime ethers have also been reported. Naito[3,8] studied some malonate-derived substrates **41.2**, prepared by stereoselective alkylation of chiral camphorsultams (Scheme 41). Diastereoselectivity was extremely high in ethyl radical addition, utilizing a Lewis acid and Et_3B. The camphorsultam itself was not the major stereocontrol element, as an experiment with **41.1** led to no stereocontrol. Minimization of allylic strain was presumed to favor the transition state shown, wherein the α-substituent R_1 blocks one face of the C=N acceptor.



41.1 R_1 = H
41.2 R_1 = benzyl

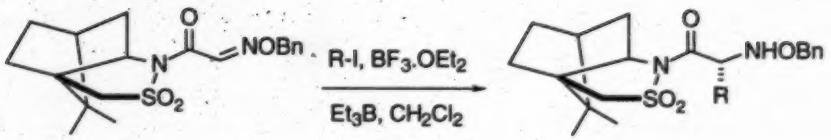
41.3 84%, dr 1.1: 1
41.4 99%, dr 40:1



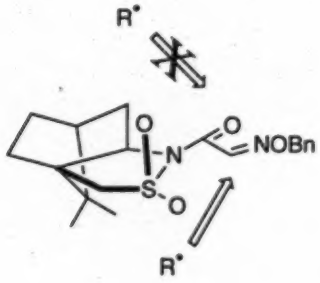
41.5

Scheme 41

Naito[39] has used camphorsultam derivatives also as an chiral auxiliary. The camphorsultam auxiliary was linked through an amide bond to the *O*-benzyloxime of glyoxylic acid as in **42.1** (Scheme 42). Compound **42.1** was then subjected to radical addition conditions, using a variety of Lewis acid promoters and alkyl iodides, along with triethylborane initiation. Under these conditions, addition of ethyl, isopropyl, cyclohexyl and *t*-butyl radicals gave amino acid derivatives **42.2** in 80-86% yield with very high diastereoselectivity. It was proposed that a sulfonamide oxygen was critical for blocking one of the approach trajectories, resulting in high diastereoselectivity.



42.1 42.2

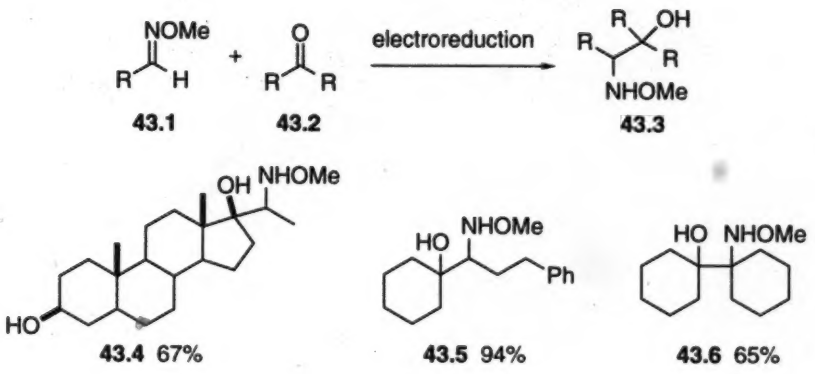


42.3

Scheme 42

A general electroreductive coupling procedure, affording 1,2-amino alcohols from ketones and oxime ethers, was reported by Shono.[40] At a constant current, using a tin cathode and a carbon anode, a mixture of oxime ether **43.1** and ketone **43.2** was converted selectively to the cross-coupled product **43.3** (Scheme 43). In 16 examples, yields of 43-98% were obtained, and a notable feature of the reaction was the tolerance of steric hindrance. Thus, a hindered steroidal ketone was coupled to form **43.4** in good yield, and cyclohexanone also underwent cross coupling to give hydroxy hydroxylamines **43.5** and **43.6**. Since the oxime ethers themselves were inert under these conditions, the selective reaction was proposed to involve initial one electron reduction of the ketones, followed by intermolecular ketyl radical anion addition to the closed-shell oxime ether

function.



Scheme 43

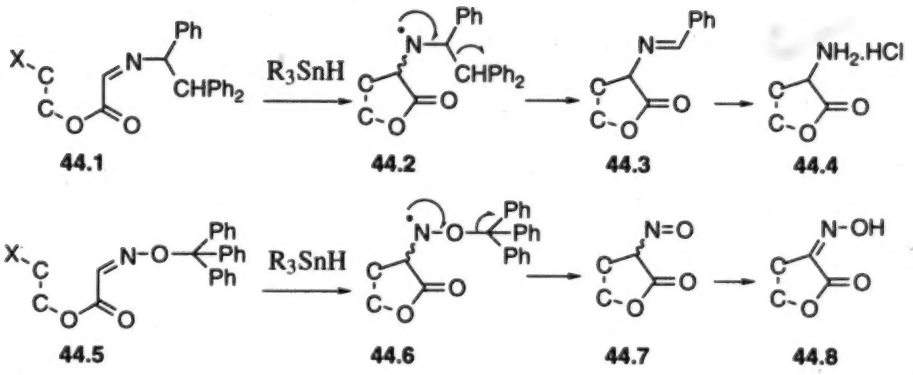
C. Conclusions

A great deal of research conducted in the field of radical addition to oxime ethers shows that such reactions constitute synthetically very useful processes. Oxime ethers are undoubtedly versatile acceptors for various types of radical, and it is clear that the future will see the development of more sophisticated synthetic applications, including asymmetric methods.

II. Results and Discussion

A. Radical Cyclization of *O*-Trityloximino Esters

During our attempts to develop a method for making α-amino acids by way of radical cyclization onto hydrazones, we recognized that it might be possible to effect closure onto an oxime C=N double bond in such a way that the double bond is retained. This would be an unusual process because normally radical addition to a double bond results in formation of a single bond, except in those cases, discussed in the previous section, where the proximal end of the double bond carries a radical leaving group. Such compounds (e.g. acyl germanes, or phenylsulfonyl oxime ethers) usually require several steps for their preparation and are not as readily accessible as simpler substances containing more common functionalities. We had previously observed (see Scheme 44 and Chapter 1 of this Thesis) that a diphenylmethyl radical can be expelled by an adjacent aminyl radical (**44.1**→**44.2**→**44.3**). By analogy, we felt that an *O*-trityloxime ester should react in the manner summarized by the sequence (**44.5**→**44.6**→**44.7**) because a trityl radical should be a very good leaving group. The nitroso product **44.7** would be expected to tautomerize so as to regenerate the oxime C=N double bond.



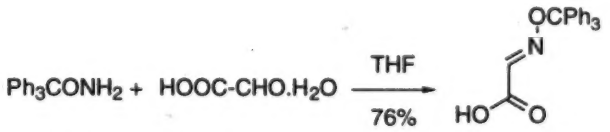
44.1 44.2 44.3 44.4

44.5 44.6 44.7 44.8

Scheme 44

As this Scheme shows, the special feature of the cyclization of trityloximino esters is that the sp^2 status of the acceptor carbon is preserved; a result that is different from the one seen in the classical cyclization of hexenyl radicals or the radical cyclization of *O*-alkyl oxime ethers.

To explore this possibility we prepared the reagent **45.3** by stirring *O*-tritylhydroxylamine and glyoxylic acid monohydrate in THF for 4 h (Scheme 45). Evaporation of the solvent and column chromatography over silica gel gave pure **45.3**, whose geometry in the solid state was established by X-ray analysis.



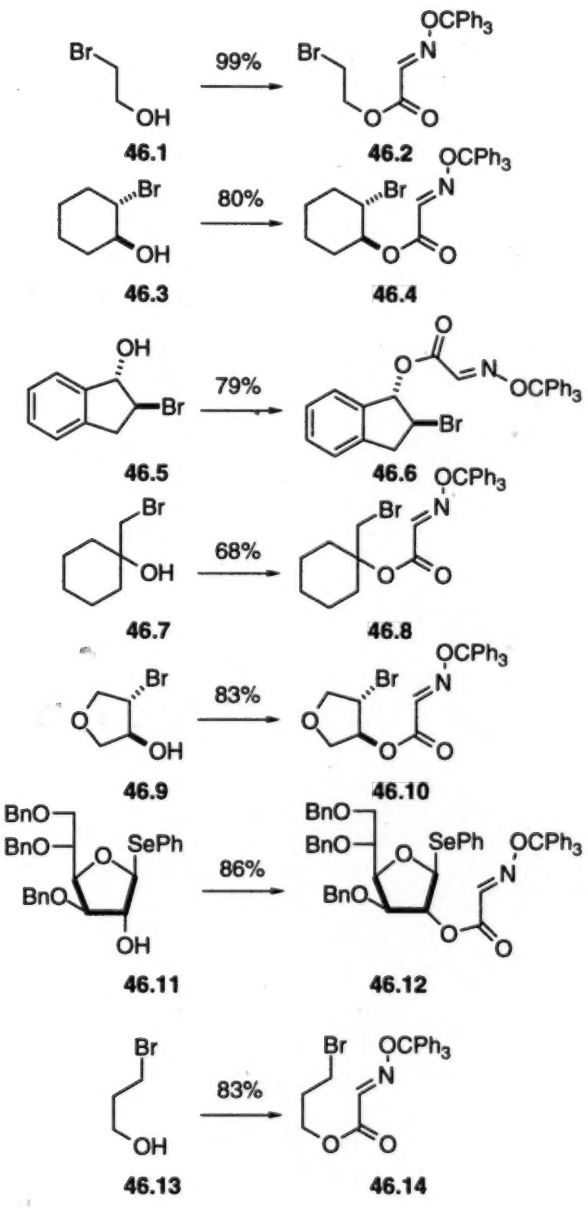
45.1 45.2 45.3

Scheme 45

Reagent **45.3** (1 mmol) reacts smoothly with alcohols (1.1

mmol) in dichloromethane in the presence of DCC (1.1 mmol) and a catalytic amount of DMAP to give the corresponding esters, after 1-26 h. A number of alcohols were examined, and we found that the yields in these esterifications are generally high, as shown in Scheme 46.

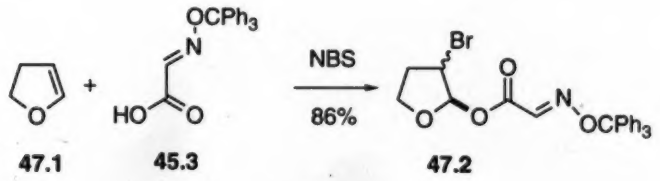
The parent alcohol for **46.7** is a known compound,[41] but one tentative structural assignment given in the literature [(1-bromocyclohexyl)methanol] is incorrect;[41a] our X-ray analysis of **46.8** establishes the actual structure.



Scheme 46

Direct esterification is not the only route to the oximino esters and, in one case (Scheme 47) we prepared the

required ester by reaction of our reagent **45.3** (1.1 mmol) with a THF solution of the enol ether **47.1** (1.0 mmol) in the presence of NBS (1.1 mmol); again the yield was high.

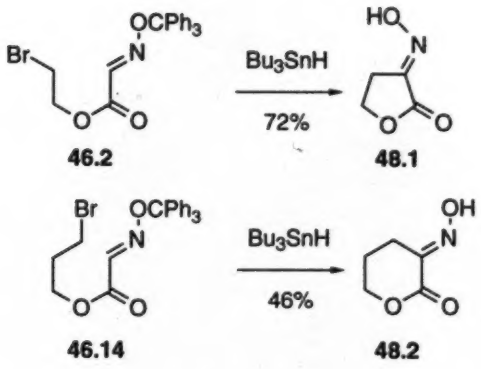


47.1 **45.3** **47.2**

Scheme 47

The radical cyclization step shown for **44.5** (Scheme 44) requires the indicated proximity of the carbon radical and the carbon-nitrogen double bond; in the event this conformation turns out to be adequately accessible because of the sufficiently low rotational barrier about an ester C(O)-O single bond.[42]

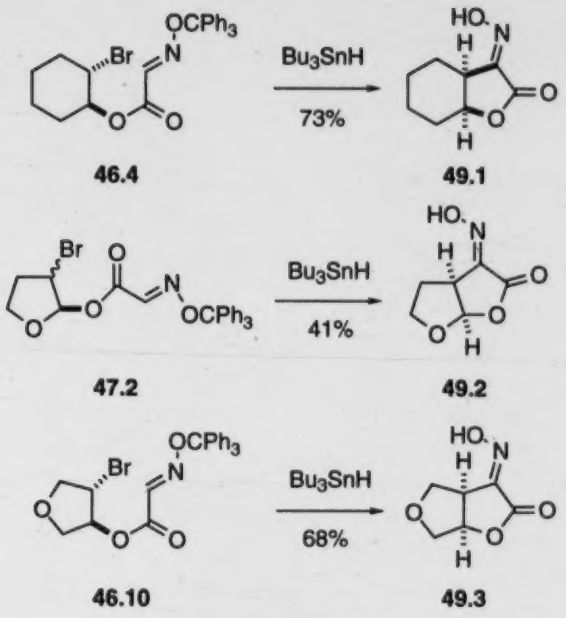
Each of our esters was found to undergo radical cyclization. The reactions were done by slow addition (ca 10 h) of separate dilute toluene solutions of tributyltin hydride (0.17 M) and AIBN (0.012 M) to a refluxing toluene solution of the ester (0.016 M). Refluxing was continued for an arbitrary period of 2 h after the end of the addition, and the products were isolated by evaporation of the solvent and flash chromatography. We normally used an excess (1.5-2.5 mmol per mmol of ester) of the stannane and 0.1-0.2 mmol AIBN per mmol of ester.



Scheme 48

Radical cyclization of **46.2** proceeded in high yield to give **48.1** (72%) by 5-*exo* closure (Scheme 48). However, radical cyclization of **46.14** by 6-*exo* closure was less efficient, and gave only 46% of **48.2**.

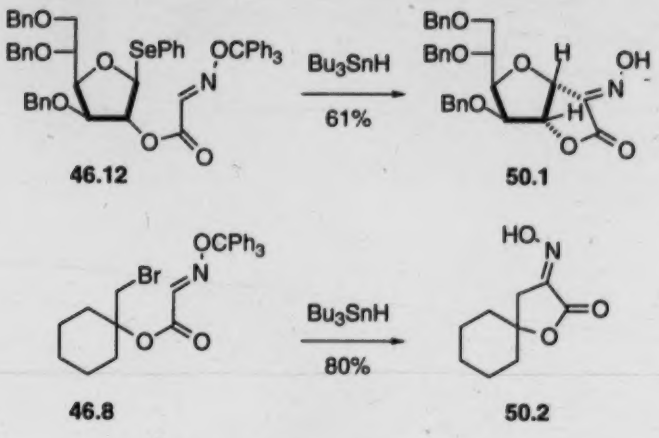
Several bicyclic [3.3.0] and [4.3.0] ring systems were also constructed by this method (Scheme 49). The ring fusion geometry in these systems is necessarily *cis*.[43]



Scheme 49

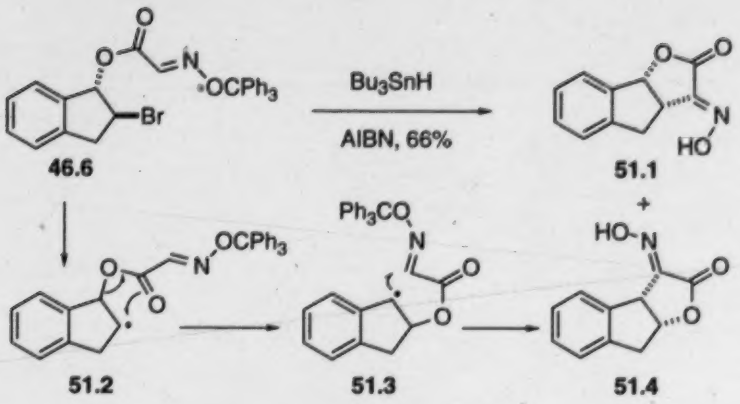
The methodology was also applied to a carbohydrate (Scheme 50). Thus, treatment of **46.12** with tributyltin hydride resulted in the sugar oximino lactone **50.1** in 61% yield.

The spirocyclic oximino lactone **50.2** was constructed, likewise, in good yield (Scheme 50).



Scheme 50

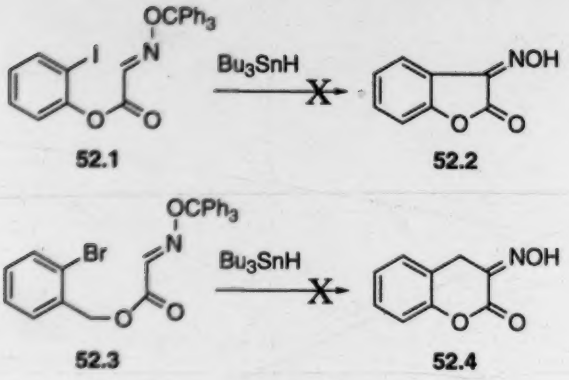
The case of **46.6** was more complicated than the other examples. When ester **46.6** was subjected to the radical cyclization, we isolated two compounds **51.1** and **51.4** in 66% yield and in a 1:2 ratio (Scheme 51). Spectral analysis of compounds **51.1** and **51.4** suggested the structures shown, although the oxime geometry is an arbitrary assignment. Compound **51.1** is the normal cyclization product. Compound **51.4** must have been formed by 1,2-acyl migration[44] of the radical derived from **46.6**, the rearrangement being driven by formation of a stable benzylic radical.



Scheme 51

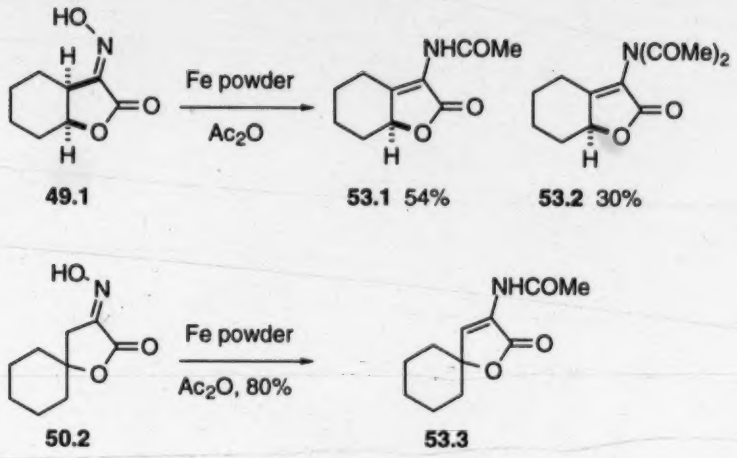
While the oxime geometry for **45.3** and **46.8** was determined by X-ray analysis, the geometries shown for the other oximes are arbitrary assignments. All the cyclization products from our *O*-trityloximino esters were single isomers.

We also prepared the two aromatic halides **52.1** and **52.3** bearing the *O*-trityloximino group. These compounds did not undergo the desired cyclization (Scheme 52); we suspect, on the basis of thin layer chromatograms, that starting material was largely recovered, but we did not isolate and definitely identify the material.



Scheme 52

At this point, we decided to investigate manipulation of the oxime function. To our surprise, this proved to be rather difficult. Several attempts to hydrolyze the oximes to the corresponding α-keto lactones or to hydrogenate the oxime to the α-amino lactones were not successful. However, we were able to partially reduce several of our oximino lactones. Thus, treatment of **49.1** with iron powder[45] in acetic anhydride at room temperature for 14 h gave a mixture of enamide **53.1** (54%) and the doubly acetylated analog **53.2** (30%). Under the same conditions, **50.2** gave **53.3** (80%), and no bisacetylated product was isolated (Scheme 53) in this case.

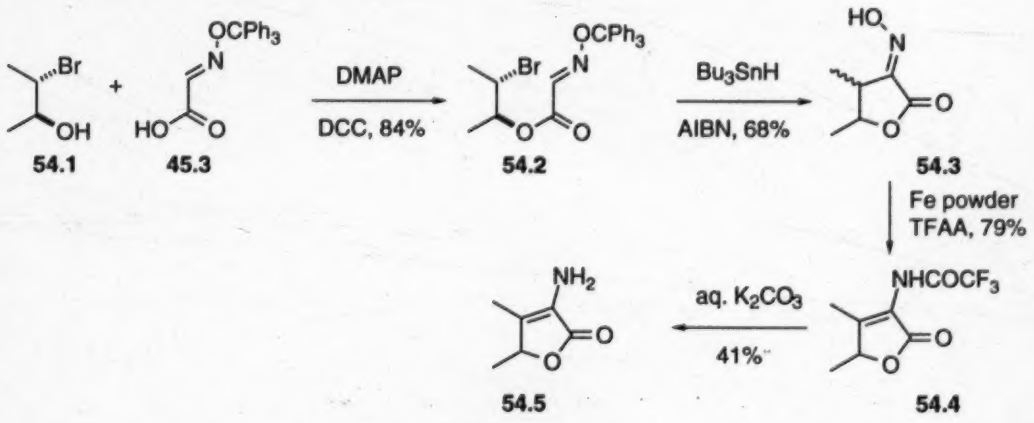


Scheme 53

This methodology of radical cyclization onto an *O*-trityloxime, followed by reduction was then applied to the synthesis of the natural product **54.5**.[46] This compound (Scheme 54) is present in the flowers of the tree *Quararibea funebris* (Llave). Extracts of the flowers have been used[47] by the Zapotec Indians of Oaxaca, Mexico, to treat a number of disorders, including some of a psychological nature, but it is not known whether **54.5** itself is biologically active. It has also been suggested that the compound may be the biosynthetic precursor of several pyrrole alkaloids present in the flower extract.[47]

The required ester was made by DCC-mediated coupling of bromoalcohol **54.1** with reagent **45.3** in 84% yield (Scheme 54). The ester was then subjected to radical cyclization using tributyltin hydride in the presence of AIBN, and the desired product **54.3** was isolated in 68% yield. This

cyclization product was obtained crystalline, and X-ray analysis showed the crystals to be composed of the *trans,E* and *cis,E* isomers in a ratio of ca 55:45; the same composition was evident from the ^{1}H NMR spectrum. Treatment of **54.3** with iron powder in trifluoroacetic anhydride gave enamide **54.4**, the fluorinated anhydride being used because we expected this choice to facilitate subsequent amide hydrolysis. Compound **54.4** was then treated with aqueous potassium carbonate to afford the natural product.

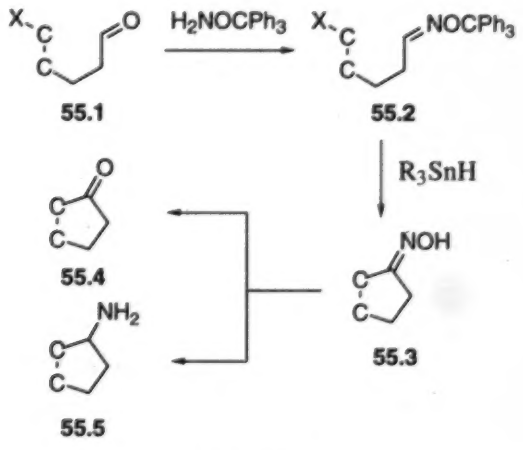


Scheme 54

B. Extension of the Methodology to Non-lactone Substrates

Some time after the above work was completed, we decided to use the method to construct non-lactone structures. An extension of this type would be useful for making oximes of cyclic ketones, and these compounds could then be converted into amines or ketones by manipulation of the oxime

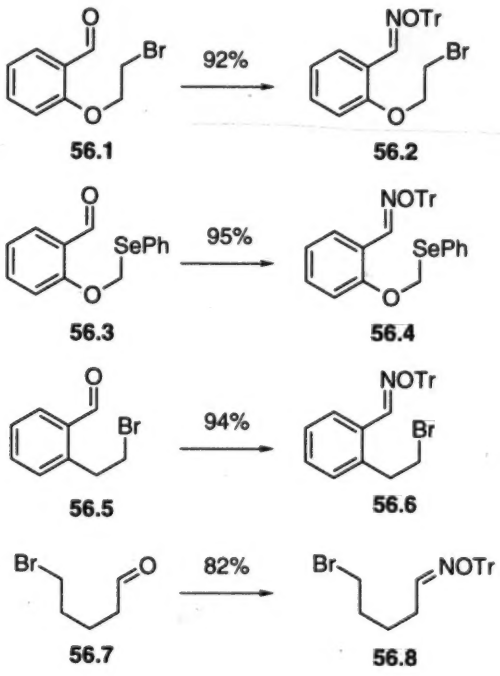
functionality (Scheme 55). Generally, carbonyl functionalities are less satisfactory as radical acceptors[1a] than oximes because of the fact that the rate of ring opening of the oxygen radical is similar to the cyclization rate. Oximes, on the other hand, are known to be better acceptors for radical reactions, as discussed in the previous section. Thus, by this method we hoped that aldehydes could be converted into the corresponding oxime derivatives, and after the radical reaction, a ketone carbonyl could be regenerated, if desired.



Scheme 55

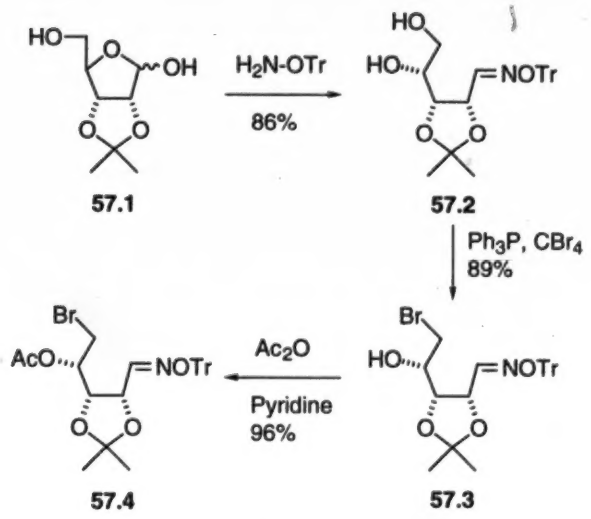
Preparation of the radical cyclization precursors i.e. the trityloximes was straightforward, and several suitable compounds were prepared by coupling of equimolar amounts of corresponding aldehydes and *O*-tritylhydroxylamine. In all cases the yields were excellent (Scheme 56). Of course, we tried the radical cyclization experiments after making each

substrate, but it is convenient to describe the preparation of all the substrates first, and then to discuss our observations on the cyclization step.



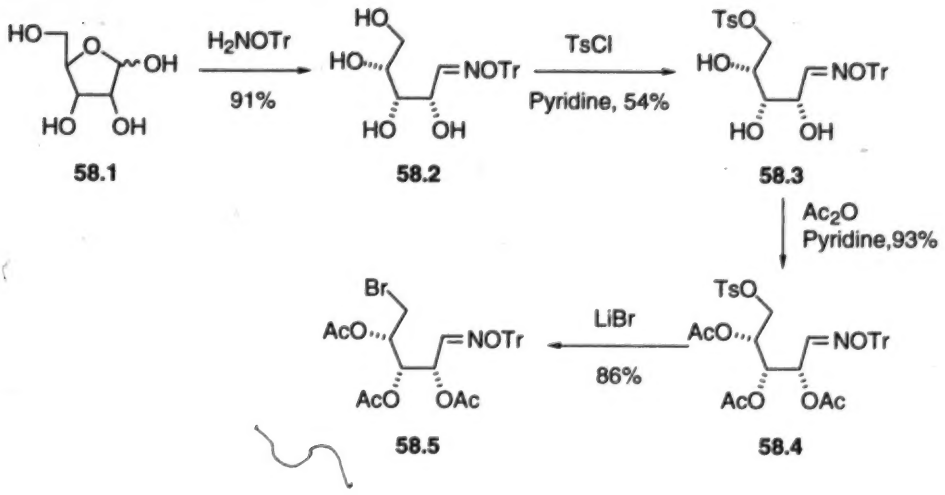
Scheme 56

However, in the case of carbohydrates the required oxime precursors were prepared in a somewhat more complicated way, as the homolyzable group was introduced after generation of the oxime. The trityloxime of the ribose derivative **57.2** was prepared by direct coupling of *O*-tritylhydroxylamine with **57.1**, and the primary hydroxyl was then converted into the corresponding bromide **57.3** (Scheme 57). Finally, acetylation of bromide **57.3** resulted in the desired product **57.4**.



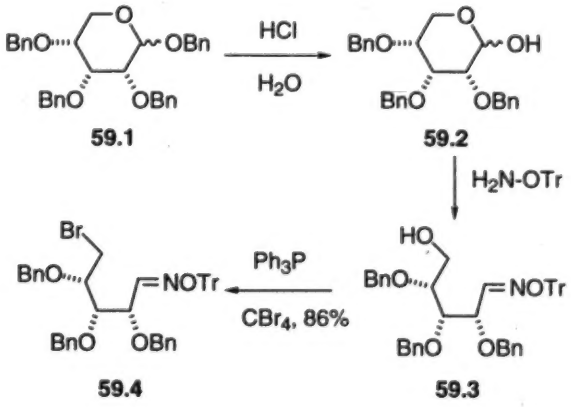
Scheme 57

The trityloxime **58.2** was prepared by coupling of *O*-tritylhydroxylamine with D-ribose **58.1**. Selective tosylation of the primary alcohol resulted in compound **58.3**, which was then converted into the triacetate **58.4** and then into bromide **58.5** by nucleophilic displacement of the tosylate, using lithium bromide (Scheme 58).



Scheme 58

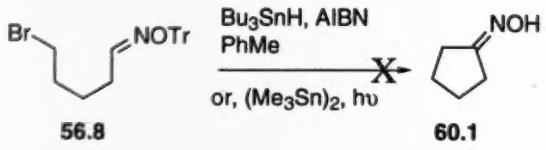
Our last carbohydrate-derived *O*-trityloxime (**59.3**) was prepared by a direct coupling with the fully benzylated ribopyranoside lactol **59.2** (Scheme 59). The resulting alcohol was then converted to the desired bromide **59.4** in usual manner.



Scheme 59

Attempted radical cyclization of compound **56.8** using

tributyltin hydride and AIBN in toluene did not produce any of desired product (Scheme 60). Irradiation of compound **56.8** in the presence of hexamethylditin in benzene also was not successful.

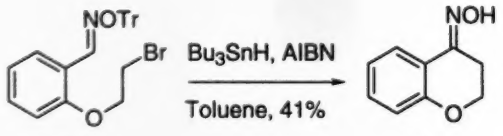


56.8 **60.1**

Scheme 60

We then decided to attempt the cyclization with a substrate where the C=N was activated (lowering of the LUMO) by a substituent, as in compound **56.2**. When the LUMO energy is lowered the C=N becomes a better radical acceptor because the SOMO-LUMO energy gap is reduced.[48] The aromatic substituent also makes the H-C=N carbon-hydrogen bond more acidic and this should favor tautomerization of the intermediate nitroso function to the oxime.

When compound **56.2** was treated with tributyltin hydride in the presence of AIBN in toluene, the desired product **61.1** was isolated in 41% yield (Scheme 61).



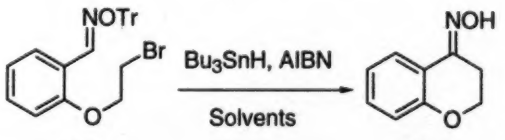
56.2 **61.1**

Scheme 61

As the above reaction did work, although not

efficiently, we decided to try to find conditions that would improve the yield.

Since oximes carry a hydroxyl group we expected that, if the radical cyclization reaction were to be done in solvents which are good hydrogen bonding acceptors, tautomerization of the intermediate nitroso compound to the oxime might be facilitated. The effect of different solvents in the cyclization reaction of **56.2** was then investigated, with the results summarized in Scheme 62.



56.2 **61.1**

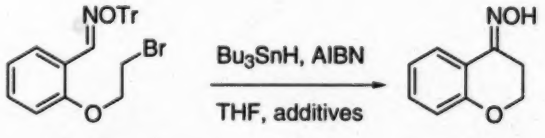
Solvents	dielectric constant	%Yield of **61.1**
Toluene	2.4	41
Dioxane	2.2	42
DMSO	46.7	43
CH_3CN	37.5	52
THP	5.5	68
DME	7.2	67
EtOAc	6.2	18
THF	7.6	71

Scheme 62

When the compound **56.2** was subjected to radical cyclization using tributyltin hydride and AIBN in THF we isolated 71% of **61.1**. Similar results were obtained when tetrahydropyran (68%) or 1,2-dimethoxyethane (67%) were used as solvents. Cyclization in dioxane, however, resulted only in a 42% yield, similar to that obtained in toluene. We had hoped that the high boiling point (100 °C) of dioxane would also serve to facilitate the tautomerization. The common

feature between dioxane and toluene, solvents that gave similar yields, is their low dielectric constants. Thus, we felt that the dielectric constant of the solvent may have some effect in these reactions, and we decided to examine solvents which have high dielectric constants and which are also good acceptors for hydrogen bonding. However, radical cyclization in acetonitrile resulted in only a 52% yield, while in dimethylsulfoxide the yield was even lower (43%).

We also investigated the effect of additives, such as *N*-methylpyrrolidone and 2-pyridone. However, in the experiments we have performed (Scheme 63), these additives clearly did not have any effect. In each experiment we added 1-1.5 mol of the additive per mole of the substrate.



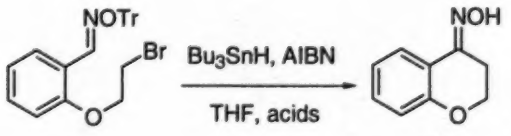
56.2 **61.1**

Additives	%Yield of **61.1**
none	71%
2-Pyridone	71%
NMP	69%

Scheme 63

The effect of acids and bases in the cyclization reactions was also studied. Use of Lewis acids in radical cyclizations is common, particularly in the reactions involving C=N double bond.[49] The Lewis acid binds with the nitrogen atom of C=N bond and makes the carbon atom more electrophilic, and thus a better radical acceptor. However,

we found that use of $BF_3.Et_2O$ produced a complex mixture, and no starting material was recovered. When moderately strong Lewis acid $Ti(OPr\text{-}i)_4$ was used we isolated 39% of the starting compound but none of the desired product. Possibly, these Lewis acids interact with the trityloxy group, although we did not isolate any products to support this assumption. Use of a weak Lewis acid such as Bu_3SnCl also failed to improve the cyclization; however, in this case unlike the others, we were able to isolate the product in similar yield (68%) to that obtained in the absence of Lewis acids (Scheme 64).



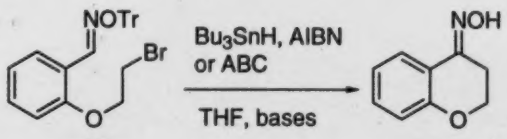
56.2 **61.1**

Acids	%Yield of **61.1**
None	71
$BF_3.OEt_2$	0
$Ti(OPr\text{-}i)_4$	0 (39% SM)
Bu_3SnCl	68

Scheme 64

Bases such as pyridine and triethylamine have been used to influence nitroso-oxime tautomerization in favor of the oxime tautomer.[50] When compound **56.2** was treated with tributyltin hydride and AIBN in THF, with pyridine as an additive (1.4 mmol per mmol of substrate), we isolated **61.1**. However, the material was contaminated with an unidentified AIBN-derived impurity. (The ^1H NMR spectrum showed a singlet

at δ 1.7, 6 H, along with the other signals for the expected product). After purification of the compound by recrystallization we isolated only 54% of the desired product (Scheme 65). When this cyclization was done using ABC [1,1'-azobis(cyclohexanecarbonitrile)] instead of AIBN as an initiator, and still in the presence of pyridine, we obtained 86% of the desired product. Use of diisopropylethylamine (Hünig's base) as an additive produced the desired product in even better yield (92%). It is not obvious why ABC leads to an improvement over AIBN; possibly, subtle steric differences between the corresponding intermediate radicals suppress some undesired pathways in the case of ABC.



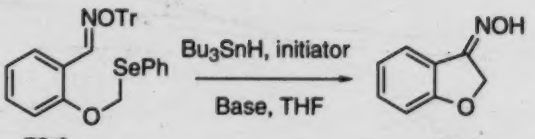
56.2 **61.1**

Bases	Initiator	Yield of **61.1**
none	AIBN	71
Pyridine	AIBN	54
Pyridine	ABC	86
i-Pr_2NEt	ABC	92

Scheme 65

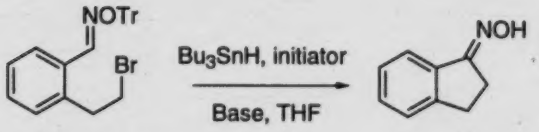
Similar results were obtained in the radical cyclization of **56.4**; in the absence of a base only 69% yield of 2,3-dihydrobenzofuran oxime **66.1** was isolated, while in the presence of diisopropylethylamine **66.1** was obtained in 91% yield. The same beneficial influence of the base was also observed in the construction of 1-indanone oxime **66.2** from

56.6 (Scheme 66).



56.4 **66.1**

Base	Initiator	%yield of **66.1**
none	AIBN	69
i-Pr_2NEt	ABC	91

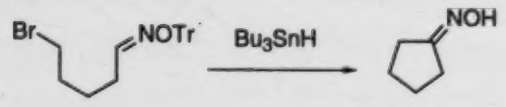


56.6 **66.2**

Base	Initiator	%yield of **66.1**
none	AIBN	67
i-Pr_2NEt	ABC	87

Scheme 66

We then decided to apply these improved reaction conditions to **56.8**, which does not have any activating group attached to the oxime (Scheme 67). Radical cyclization of this substrate in toluene had not produced any of the desired product previously (Scheme 60), however, when the radical reaction was done in THF we isolated cyclopentanone oxime in 41% yield. Surprisingly, the radical reaction in THF with diisopropylethylamine did not improve the yield further.

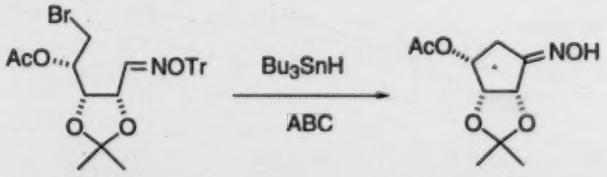


56.8 60.1

Solvent	Initiator	Base	% yield of 60.1
Toluene	AIBN	none	0
THF	AIBN	none	41
THF	ABC	*i*-Pr_2NEt	41

Scheme 67

At this point, we arbitrarily decided to examine some carbohydrate substrates, prompted, perhaps, by the fact that if our cyclization were successful it would provide a route to optically pure functionalized cyclopentanes. Carbohydrate oximes are known to be good acceptors for radical cyclization reactions,[51] and so we decided to examine a few carbohydrate *O*-trityloximes. When compound **57.4** was subjected to radical cyclization in THF and in the presence of Hünig's base and ABC, the desired product **68.1** was obtained in 93% yield (Scheme 68).



57.4 68.1

Solvent	Base	% yield of 68.1
THF	*i*-Pr_2NEt	93
C_6H_6	none	74

Scheme 68

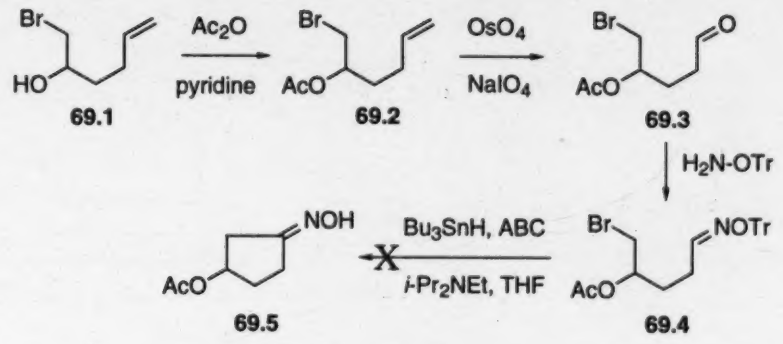
Interestingly, the desired product was isolated in good

yield (74%) even in benzene as a solvent and in the absence of a base. In this case, the initiator was ABC. Evidently, the substance has a natural tendency to undergo efficient ring closure, and here there are two obvious features in compound **57.4** which might facilitate the cyclization:

(a) the presence of the acetoxy functionality β to the radical center, may have some effect on the ease of formation and/or the reactivity of the initial radical. This so-called β-oxygen effect is currently the subject of debate,[52] and the nature of the effect on the radical is not clear.

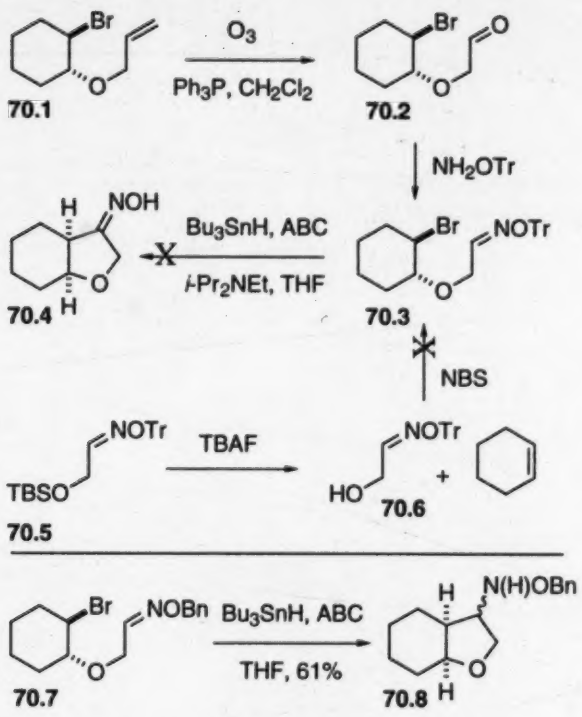
(b) the presence of the isopropylidene ketal ring, reduces the flexibility of the molecule and favors those conformations in which the reacting centers are close together.

In order to see whether the substituent at the β-position to the radical center can independently influence the radical cyclization, we prepared substrate **69.4**, using the reactions shown in Scheme 69. To our surprise, when **69.4** was treated with tributyltin hydride and ABC in toluene and in the presence of Hünig's base, none of the desired product was obtained (Scheme 69). Even more surprising was the fact that 56% of the starting material **69.4** was recovered.



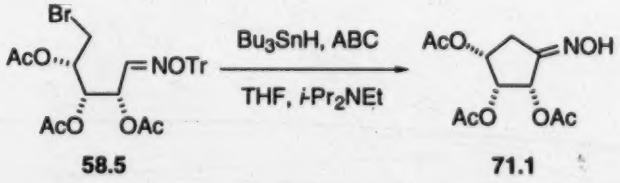
Scheme 69

At this point we examined more closely the second feature of the carbohydrate **57.4**, namely the conformational restrictions imposed by the presence of a ring. To this end we prepared substrate **70.3**, in which the substituents are attached to a cyclohexane ring so as to restrict somewhat their conformational freedom (Scheme 70). An attempt to make radical precursor **70.3** directly by reacting 2-hydroxyacetaldehyde *O*-trityloxime **70.6** with cyclohexene in the presence of NBS was not successful. However, the desired compound could be prepared in 94% yield by coupling the corresponding aldehyde **70.2** with *O*-tritylhydroxylamine. Radical cyclization of **70.3** in THF and in the presence of base, did not produce any of the desired product, instead, 75% of starting material **70.3** was recovered. However, radical cyclization of the corresponding *O*-benzyl oxime **70.7**, which has similar structural features as **70.8**, went smoothly in THF (61% of the desired product) (Scheme 70).



Scheme 70

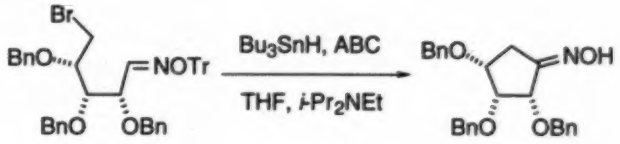
Later, we found that the presence of an isopropylidene ketal ring was not necessary for successful radical cyclization in the carbohydrate series. Thus, radical cyclization of compound **58.5** in THF and in the presence of base resulted in 85% of the desired compound **71.1** (Scheme 71).



58.5 71.1

Scheme 71

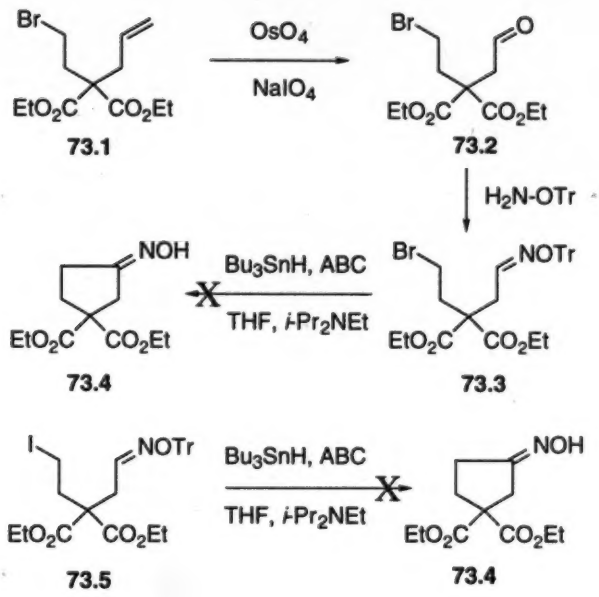
Radical cyclization of **59.4**, in which the oxygens are protected by benzyl groups also went smoothly (92% yield) (Scheme 72), although, in this case a large excess (6 equiv.) of tributyltin hydride was needed for complete disappearance of the starting material.



59.4 **72.1**

Scheme 72

As it was not clear to what extent the number or relative disposition or nature of the substituents were influencing the outcome of the cyclizations with carbohydrates, we decided to establish whether an isolated Thorpe-Ingold effect[53] could also facilitate ring closure. Therefore, we constructed the radical cyclization precursor **73.3** with two substituents on the same carbon (Scheme 73). However, attempted radical cyclization of **73.3** in THF and in the presence of base did not produce any of the desired product. The high field ^{1}H NMR spectrum of the crude reaction mixture showed the presence of the starting bromide **73.3**, but we made no attempt to isolate the material to determine the percentage recovery.

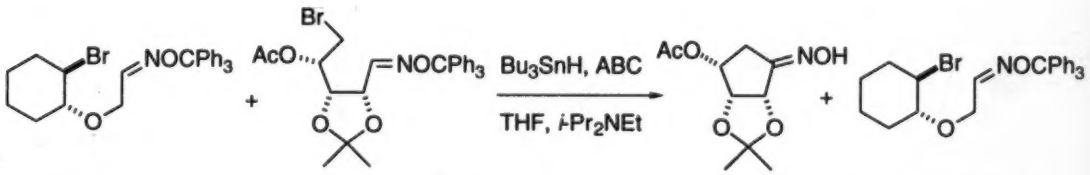


Scheme 73

We also made the corresponding iodide **73.5**. This time, attempted radical cyclization in THF gave a complex mixture as judged by TLC, and 20% of the starting oxime was isolated (Scheme 73).

One of the intriguing features of these radical cyclizations is the recovery of the starting material instead of the normally expected corresponding reduced product. The usual explanation for this kind of behavior in radical chemistry is the presence in the reaction mixture of a radical inhibitor which inhibits radical chain propagation. We therefore decided to do a control experiment to see whether the substrates that are not cyclizing under our conditions contain some type of radical inhibitor. We had earlier found that substrate **57.4** readily cyclized to give

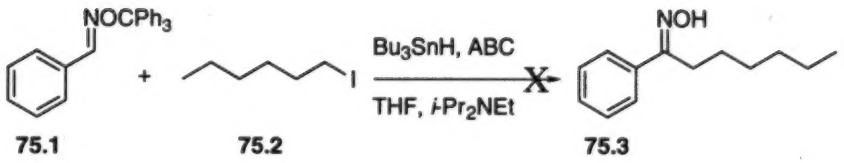
the desired product **68.1** (Scheme 68), whereas in the case of substrate **70.3** a large excess of starting compound was isolated (Scheme 70). A similar result was obtained in an experiment (scheme 74) in which equimolar amounts of **70.3** and **70.4** were treated with Bu_3SnH (8 equiv.), ABC (0.2 equiv.) and *i*-Pr_2NEt (8 equiv.) in THF. Since **68.1** cyclized (in 76% yield) this experiment proves that no radical inhibitors were present in the mixture, and the lack of reactivity of **70.3** must be due to some other cause.



70.3 **57.4** **68.1** 76% **70.3** 65% (SM)

Scheme 74

An intermolecular version of our reaction was not successful (Scheme 75). Thus, when benzaldehyde trityloxime **75.1** was treated with an excess of hexyl iodide under our best conditions, no addition product was isolated. We suspect that the starting oxime was recovered unchanged, as evaporation of the solvent and flash chromatography of the residue gave an impure sample of an oxime with the signal at δ 8.23, characteristic of **75.1**, but we did not further purify the material to make a definite identification.



75.1 75.2 75.3

Scheme 75

Because of the fact that some of our substrates do not undergo cyclization with tin hydrides we intend to reexamine compounds **56.2** and **70.3** in the presence of alternatives to tin hydrides, and this work has already started, and is included in the Appendix. Using $(Me_3Si)_3SiH$ and ABC in THF and in the presence of Hünig's base, we obtained only recovered starting material (ca 98%). Current work is underway to complete the appropriate control experiments. These include the use of $(Me_3Si)_3SiH$ in the absence of Hünig's base, and use of the silane on a mixture of **56.2** and **70.3**. It will also be appropriate to try $(EtO)_2P(O)H$ in place of the usual stannane.

C. Conclusions

A general methodology for the preparation of various oximino lactones by stannane-induced radical cyclization of *O*-trityloximino esters has been developed. Oximino lactones can be further converted into enamides, and such a transformation was used to make a natural product. This methodology was extended to certain non-lactone substrates, and in these cases we demonstrated the influence of various solvents and base additives on the radical cyclization. The

mechanism of the *O*-trityloxime cyclizations may be more complicated than the simple radical cyclization shown in Scheme 44, as that pathway does not account for the unexpected failure of the cyclization in a few cases. Further mechanistic studies are underway in this laboratory.

III. Experimental Section

General Procedures. The same general procedures were used as described in Part 1 of this Thesis.

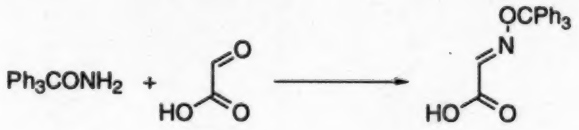
General procedure for coupling of alcohols with reagent 45.3.

Reagent **45.3** (1.0 equivalent) was added to a stirred mixture of the alcohol (1.1 equivalent), DCC (1.1 equivalent) and DMAP (0.10 equivalent) in dry CH_2Cl_2. Stirring was continued for 12 h, and the mixture was then filtered. The insoluble material was washed with dry CH_2Cl_2 and the combined filtrates were evaporated to give a residue which was processed as described for the individual experiments.

General procedure for Radical Cyclization.

The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The system was flushed with argon and dry PhMe was injected into the flask. The solution was heated to 110 °C, and solutions of Bu_3SnH and AIBN in PhMe were injected simultaneously by syringe pump over 10 h. Refluxing was continued for arbitrary period of 2 h after the end of the addition. The reaction mixture was cooled and the solvent evaporated to give a residue which was processed as described for the individual experiments.

(2*E*)-[(Triphenylmethoxy)imino]acetic Acid (45.3).

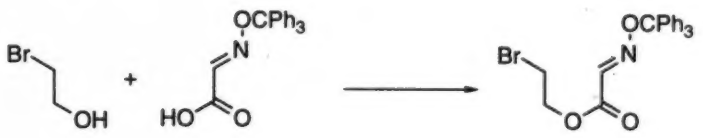


45.1 **45.2** **45.3**

Dry THF (15 mL) was added to a stirred mixture of *O*-tritylhydroxylamine[54] (1.522 g, 5.534 mmol) and glyoxylic acid monohydrate (0.5095 g, 5.535 mmol). Stirring was continued for 4 h (TLC control, 30% EtOAc-hexane), and the solvent was then evaporated. Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 30% EtOAc-hexane, gave **45.3** (1.4 g, 76%) as a white, crystalline solid: mp 165-166 °C; FTIR (CH_2Cl_2 cast) 3059, 2624, 1713 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 7.1-7.5 (m, 15 H), 7.8 (s, 1 H), 10.1-10.5 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 94.0 (s'), 128.1 (d'), 128.2 (d'), 129.4 (d'), 141.1 (d'), 143.5 (s'), 165.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{21}H_{17}NNaO_3$ (M + Na) 354.1106, found 354.1108.

X-Ray analysis established the *E*-geometry for the oxime.

2-Bromoethyl [(Triphenylmethoxy)imino]acetate (46.2).

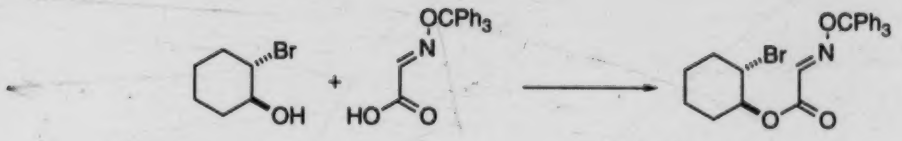


46.1 **45.3** **46.2**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (469.3 mg, 1.418 mmol), DCC (321.8 mg, 1.559 mmol), DMAP (20 mg, 0.14 mmol) and 2-bromoethanol (194.8 mg, 1.559 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel using 10% EtOAc-hexane, gave ester **46.2** (615.9 mg, 99%) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3058, 3034, 1746, 1726 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.58 (t, J = 6.05 Hz, 2 H), 4.51 (t, J = 6.05 Hz, 2 H), 7.35-7.51 (m, 15 H), 7.88 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 30.4 (t'), 65.5 (t'), 95.2 (s'), 129.7 (d'), 129.8 (d'), 131.2 (d'), 143.3 (d'), 145.4 (s'), 163.1 (s'); exact mass (electrospray) m/z calcd for $C_{23}H_{20}{}^{79}BrNNaO_3$ (M + Na) 460.0524, found 460.0522.

The oxime geometry was not determined.

trans-2-Bromocyclohexyl [(Triphenylmethoxy)-imino]acetate (46.4).

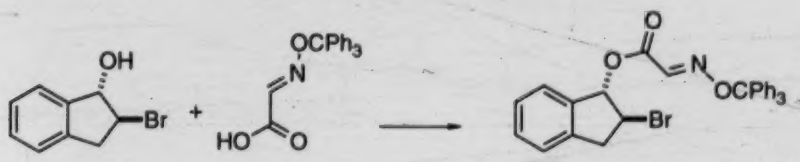


46.3 **45.3** **46.4**

The general procedure for coupling alcohols with **1** was followed, using **45.3** (401.2 mg, 1.212 mmol), DCC (274.4 mg, 1.329 mmol), DMAP (14.8 mg, 0.121 mmol) and trans-2-bromocyclohexanol[55] **46.3** (236.7 mg, 1.329 mmol) in CH_2Cl_2 (15 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 10% EtOAc-hexane, gave ester **46.4** (472.4 mg, 80%) as a crystalline solid: mp 169-172 °C; FTIR (CH_2Cl_2 cast) 3058, 3034, 2940, 2862, 1744, 1722 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.24-2.46 (m, 8 H), 4.02-4.18 (m, 1 H), 4.94-5.11 (m, 1 H), 7.34-7.43 (m, 15 H), 7.8 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 25.0 (t'), 27.1 (t'), 32.6 (t'), 37.2 (t'), 54.2 (d'), 78.8 (d'), 95.0 (s'), 129.6 (d'), 129.7 (d'), 131.2 (d'), 143.6 (d'), 145.4 (s'), 162.5 (s'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{26}{}^{79}BrNNaO_3$ (M + Na) 514.0993, found 514.1000.

The oxime geometry was not determined.

trans-2-Bromo-2,3-dihydro-1*H*-inden-1-yl [(Triphenylmethoxy)imino]acetate (46.6).

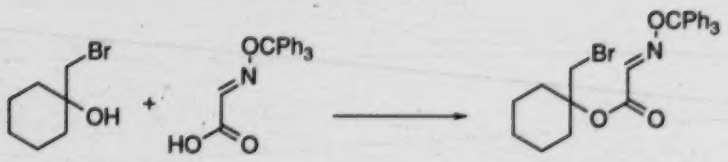


46.5 **45.3** **46.6**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (216.7 mg, 0.6546 mmol), DCC (148.5 mg, 0.7197 mmol), DMAP (8 mg, 0.1 mmol) and alcohol **46.5** (Aldrich) (153.4 mg, 0.7199 mmol) in CH_2Cl_2 (10 mL). After evaporation of the solvent, MeOH (5 mL) was added to the residue, and the resulting precipitate was filtered off and washed with MeOH (2 x 5 mL) to give **46.6** (268 mg, 79%) as a crystalline solid: mp 167-169 °C; FTIR (CH_2Cl_2 cast) 3057, 3033, 1743, 1721 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.31 (dd, J = 17.2, 3.9 Hz, 1 H), 3.71 (dd, J = 17.2, 6.5 Hz, 1 H), 4.55 (quintet, J = 3.3 Hz, 1 H), 6.38 (d, J = 3.1 Hz, 1 H), 7.2-7.45 (m, 19 H), 7.75 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 Hz), 41.9 (t'), 50.2 (d'), 85.2 (d'), 93.6 (s'), 125.3 (d'), 126.5 (d'), 128.0 (d'), 128.1 (d'), 129.5 (d'), 130.3 (d'), 137.9 (s'), 141.5 (d'), 142.0 (s'), 143.7 (s'), 161.3 (s'); exact mass (electrospray) m/z calcd for $C_{30}H_{24}{}^{79}BrNNaO_3$ (M + Na) 548.0837, found 548.0839.

The oxime geometry was not determined.

(*E*)-1-(Bromomethyl)cyclohexyl [(Triphenylmethoxy)imino]acetate (46.8).

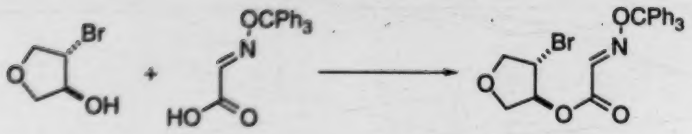


46.7 **45.3** **46.8**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (201.4 mg, 0.6084 mmol), DCC (138.1 mg, 0.6693 mmol), DMAP (7.5 mg, 0.061 mmol), and alcohol **46.7**[41] (128.7 mg, 0.6703 mmol) in CH_2Cl_2 (8 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 5% EtOAc-hexane, gave **46.8** (208.7 mg, 68%), as a crystalline solid: mp 122-123 °C; FTIR (CH_2Cl_2 cast) 3087, 3058, 3034, 2936, 1812, 1739, 1717 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.18-1.71 (m, 8 H), 2.21-2.49 (m, 2 H), 3.95 (s, 2 H), 7.33-7.48 (m, 15 H), 7.78 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 21.8 (t'), 25.5 (t'), 33.6 (t'), 39.0 (t'), 82.9 (t'), 93.5 (s'), 127.9 (d'), 128.1 (d'), 129.6 (d'), 142.4 (d'), 143.9 (s'), 160.9 (s'), exact mass (electrospray) *m/z* calcd for $C_{28}H_{28}{}^{79}BrNNaO_3$ (M + Na) 528.1150, found 528.1143.

X-Ray analysis established the oxime geometry.

trans-4-Bromotetrahydro-3-furanyl [(Triphenylmethoxy)imino]acetate (46.10).

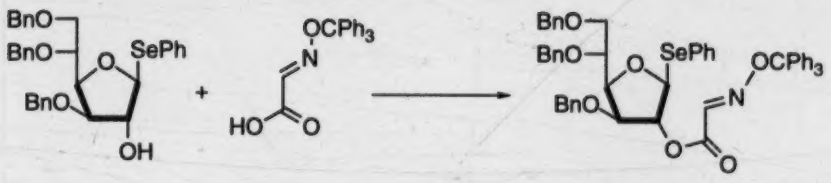


46.9 **45.3** **46.10**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (741.4 mg, 2.239 mmol), DCC (506.5 mg, 2.455 mmol), DMAP (28 mg, 0.23 mmol), and alcohol **46.9**[56] (407.5 mg, 2.455 mmol) in CH_2Cl_2 (20 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 10% EtOAc-hexane, gave **46.10** (883.8 mg, 83%) as a crystalline solid: mp 125-126 °C; FTIR (CH_2Cl_2 cast) 3057, 3023, 2859, 1747, 1726 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.88 (dd, J = 10.7, 2.1 Hz, 1 H) 4.08 (dd, J = 10.7, 2.1 Hz, 1 H) 4.18-4.38 (m, 3 H), 5.44 (dt, J = 3.2, 1.2 Hz, 1 H), 7.27-7.39 (m, 15 H), 7.7 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 48.4 (d'), 71.4 (t'), 74.9 (t'), 81.4 (d'), 93.8 (s'), 128.0 (d'), 128.1 (d'), 129.5 (d'), 141.1 (d'), 143.6 (s'), 160.9 (s'); exact mass (electrospray) m/z calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ (M + Na) 502.0629, found 502.0628.

We tentatively assign the trans stereochemistry on the basis of the splitting pattern for the C**H**OC(O) ^1H NMR signal at δ 5.44. The oxime geometry was not determined.

2-[[(Triphenylmethoxy)imino]acetyl Phenyl 3,5,6-Tris-*O*-(phenylmethyl)-1-seleno-α-L-idofuranoside (46.12).

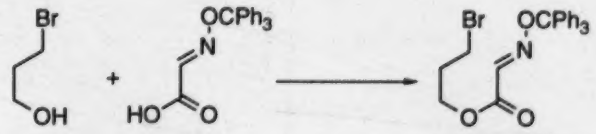


46.11 **45.3** **46.12**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (612.4 mg, 1.851 mmol), DCC (413 mg, 2.01 mmol), DMAP (24 mg, 0.19 mmol) and alcohol **46.11**[57] (1.1977 g, 2.0334 mmol) in CH_2Cl_2 (18 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 10% EtOAc-hexane, gave **46.12** (1.435 g, 86%) as a foam: FTIR (CH_2Cl_2 cast) 3059, 3030, 2862, 1747, 1725 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 3.8 (dd, *J* = 10.7, 4.5 Hz, 1 H), 4.01 (d, *J* = 10.6 Hz, 1 H), 4.15-4.33 (m, 2 H), 4.39 (dd, *J* = 9.2, 3.8 Hz, 1 H), 4.58 (d, *J* = 4.64 Hz, 1 H), 4.65 (d, *J* = 5.5 Hz, 3 H), 4.82 (d, *J* = 11.3 Hz, 1 H), 4.93 (d, *J* = 11.3 Hz, 1 H), 5.74 (s, 1 H), 5.83 (s, 1 H), 7.26-7.74 (m, 35 H), 7.78 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 70.5 (t'), 72.6 (t'), 72.8 (t'), 73.7 (t'), 76.3 (d'), 80.8 (d'), 81.9 (d'), 82.0 (d'), 87.0 (d'), 93.8 (s'), 127.8 (d'), 127.9 (d'), 128.0 (d'), 128.2 (d'), 128.3 (d'), 128.6 (d'), 128.7 (d'), 129.5 (d'), 131.6 (s'), 134.0 (d'), 137.8 (s'), 139.1 (s'), 139.3 (s'), 141.0 (d'), 143.6 (s'), 160.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{54}H_{49}NNaO_7{}^{80}Se$ (M + Na) 926.2572, found 926.2575.

The oxime geometry was not determined.

3-Bromopropyl [(Triphenylmethoxy)imino]acetate (46.14).



46.13 **45.3** **46.14**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (496.2 mg, 1.499 mmol), DCC (340.3 mg, 1.649 mmol), DMAP (18.4 mg, 0.151 mmol), and 3-bromopropanol **46.13** (229.4 mg, 1.651 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 10% EtOAc-hexane, gave **46.14** (560 mg, 83%) as a colorless oil: FTIR (CH_2Cl_2, cast) 3058, 3034, 2965, 1744, 1724 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 2.25 (quintet, J = 6.3 Hz, 2 H), 3.49 (t, J = 6.5 Hz, 2 H), 4.38 (t, J = 6.0 Hz, 2 H), 7.37-7.55 (m, 15 H), 7.87 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 31.4 (t'), 33.5 (t'), 65.0 (t'), 95.2 (s'), 129.3 (d'), 129.7 (d'), 129.8 (d'), 131.2 (d'), 143.4 (d'), 145.5 (s'), 163.5 (s'); exact mass m/z (electrospray) calcd for $C_{24}H_{22}{}^{79}BrNNaO_3$ (M + Na) 474.0680, found 474.0678.

The oxime geometry was not determined.

cis- and trans-3-Bromotetrahydro-2-furanyl [(Triphenylmethoxy)imino]acetate (47.2).

47.1 **45.3** **47.2**

NBS (304.4 mg, 1.710 mmol) was added to a stirred and cooled (-15 °C, ice-salt bath) solution of dihydrofuran **47.1** (109 mg, 1.56 mmol) and **45.3** (566.2 mg, 1.710 mmol). Stirring was continued for 2 h (-15 °C), and the mixture was left in a freezer (-20 °C) overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.7 x 34 cm), using 10% EtOAc-hexane, gave two isomers of **47.2**. The chromatographically less polar isomer (441 mg, 61%) and the more polar isomer (178 mg, 25%) were each obtained as a foam. The less polar isomer had: FTIR (CH_2Cl_2 cast) 3058, 3024, 2904, 1729 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.22-2.38 (m, 1 H), 2.5-2.64 (m, 1 H), 4.18-4.36 (m, 2 H), 4.40 (d, J = 5.37 Hz, 1 H), 6.5 (s, 1 H), 7.32-7.57 (m, 15 H), 7.79 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 33.4 (t'), 49.5 (d'), 68.9 (t'), 93.8 (s'), 103.8 (d'), 128.3 (d'), 128.4 (d'), 129.7 (d'), 141.4 (d'), 143.8 (s'), 160.6 (s'); exact mass (electrospray) m/z calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ (M + Na) 502.0629, found 502.0622.

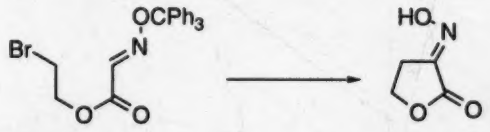
We tentatively assign cis stereochemistry on the basis of the negligible coupling for the signal at δ 6.5. The oxime geometry was not determined.

The more polar isomer had: FTIR (CH_2Cl_2 cast) 3058,

3024, 2906, 1749, 1730 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 2.19-2.35 (m, 1 H), 2.43-2.59 (m, 1 H), 3.95 (q, *J* = 8.1 Hz, 1 H), 4.08 (td, *J* = 8.9, 3.8 Hz, 1 H), 4.17-4.26 (m, 1 H), 6.38 (d, *J* = 3.9 Hz, 1 H), 7.32-7.44 (m, 15 H), 7.8 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 32.6 (t'), 44.0 (d'), 68.3 (t'), 93.8 (s'), 96.8 (d'), 128.05 (d'), 128.2 (d'), 129.7 (d'), 141.3 (d'), 143.8 (s'), 160.9 (s'); exact mass (electrospray) *m/z* calcd for $C_{25}H_{22}{}^{79}BrNNaO_4$ (M + Na) 502.0629, found 502.0637.

We tentatively assign trans stereochemistry on the basis of the coupling constant for the signal at δ 6.6.38, the *J* value being larger than for the other isomer. The oxime geometry was not determined.

Dihydro-2,3-furandione Oxime (48.1).



46.2 **48.1**

The general procedure for radical cyclization was followed, using **46.2** (592 mg, 1.35 mmol) in PhMe (85 mL), Bu_3SnH (0.595 mg, 2.04 mmol) in PhMe (11 mL), and AIBN (22 mg, 0.14 mmol) in PhMe (11 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 60% EtOAc-hexane, gave **48.1**[58] (111 mg, 72%) as a crystalline solid: mp 185-187 °C (Lit.[58c] mp 184-186 °C); FTIR (USCOPE) 3258, 2937, 2430 cm^{-1}; ^1H NMR (CD_3OD, 200 MHz) δ 2.95 (t, *J* = 7.3 Hz, 2

H), 4.51 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (CD_3OD, 50.3 MHz) 24.9 (t'), 67.1 (t') 147.9 (s'), 168.8 (t'); exact mass m/z calculated for $C_4H_5NO_3$ 115.0269, found 115.0271. Although compound **48.1** has been reported, the oxime geometry was not specified, and we did not establish it.

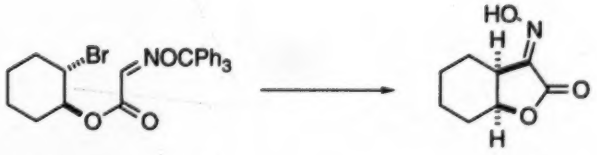
Dihydro-2*H*-pyran-2,3(4*H*)-dione 3-Oxime (48.2).

46.14 **48.2**

The general procedure for radical cyclization was followed, using **46.14** (360 mg, 0.798 mmol) in PhMe (50 mL), Bu_3SnH (460 mg, 1.58 mmol) in PhMe (10.0 mL), and AIBN (26 mg, 0.16 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 40% EtOAc-hexane, gave **48.2** (48.1 mg, 46%) as a colorless oil. The product was mainly one isomer with only a trace of the second isomer. However, when the material was stored in MeOH overnight an ca 1:1 mixture of isomers were obtained and after storage for several days in MeOH the originally minor isomer had become the major isomer. The ca 1:1 mixture of isomers had: FTIR (MeOH cast) 3405, 2945, 2530, 1723, 1631 cm^{-1}; ^1H NMR (CD_3OD, 400 MHz), δ 1.66-1.78 (m, 0.86 H), 1.93-2.06 (m, 1.2 H), 2.65 (t, J = 7.7 Hz, 0.88 H), 2.78 (t, J = 6.9 Hz, 1.14 H), 3.55 (t, J = 6.6 Hz, 0.85 H), 4.38 (t, J =

5.2 Hz, 1.05 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 22.1 (t'), 22.4 (t'), 23.7 (t'), 29.9 (t'), 62.7 (t'), 70.2 (t'), 148.6 (s'), 153.3 (s'), 164.3 (s'), 166.1 (s'); exact mass *m/z* calcd for $C_5H_7NO_3$ 129.0426, found 129.0426.

(3aα,7aα)-Hexahydro-2,3-benzofurandione 3-Oxime (49.1).

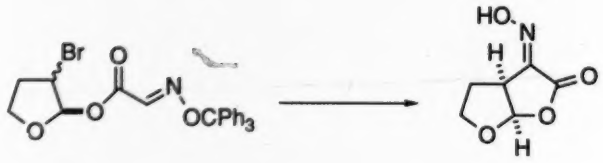


46.4 **49.1**

The general procedure for radical cyclization was followed, using **46.4** (560 mg, 1.14 mmol) in PhMe (70 mL), Bu_3SnH (663.8 mg, 12.28 mmol) in PhMe (10 mL), and AIBN (37 mg, 0.23 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 30% EtOAc-hexane, gave **49.1** (141 mg, 73%) as a crystalline solid: mp 102-105 °C; FTIR (CH_2Cl_2 cast) 3228, 2939, 2861, 1764 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) 1.12-2.22 (m, 8 H), 3.29-3.55 (m, 1 H), 4.47-4.70 (m, 1 H), 9.8-10.2 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) 19.1 (t'), 22.1 (t'), 23.3 (t'), 27.2 (t'), 36.9 (d'), 77.1 (d'), 153.7 (s'), 166.6 (s'); exact mass (electrospray) *m/z* calcd for $C_8H_{11}NNaO_3$ (M + Na) 192.0636, found 192.0638.

The oxime geometry was not determined.

(3aα,6aα)-Furo[2,3-b]furan-2,3-dione 3-Oxime (49.2).

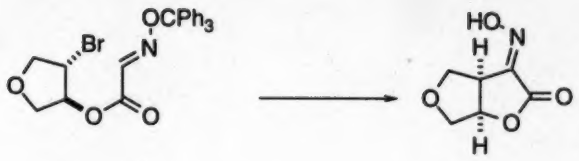


47.2 **49.2**

The general procedure for radical cyclization was followed, using the mixture of isomers of **47.2** (580 mg, 1.21 mmol) in PhMe (75 mL), Bu_3SnH (705 mg, 2.42 mmol) in PhMe (12 mL), and AIBN (30 mg, 0.18 mmol) in PhMe (12 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 50% EtOAc-hexane, gave **49.2** (76 mg, 41%) as a crystalline solid: mp 163-165 °C; FTIR (acetone cast) 3300, 3109, 2997, 2968, 2910, 2886, 1767 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 2.14-2.29 (m, 2 H), 3.68-3.78 (m, 1 H), 3.86-3.92 (m, 1 H), 4.51-4.13 (m, 1 H), 6.19 (d, J = 5.4 Hz, 1 H), 11.8-12.21 (br s, 1 H); ^{13}C NMR (CD_3OD, 100.6 MHz) δ 29.9 (t'), 42.3 (d'), 68.6 (t'), 107.6 (d'), 150.1 (s'), 166.9 (s'); exact mass (electrospray) m/z calcd for $C_6H_7NNaO_4$ (M + Na) 180.0272, found 180.0271.

The oxime geometry was not determined.

(3aα,6aα)-Tetrahydrofuro[3,4-b]furan-2,3-dione 3-Oxime (49.3).

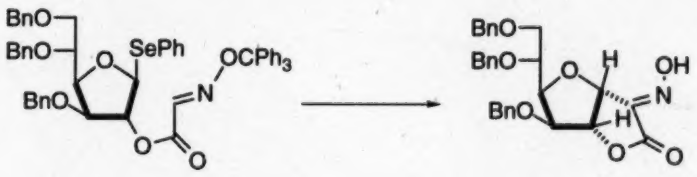


46.10 **49.3**

The general procedure for radical cyclization was followed, using **46.10** (801.6 mg, 1.673 mmol) in PhMe (104 mL), Bu_3SnH (731 mg, 2.51 mmol) in PhMe (14 mL), and AIBN (28 mg, 0.17 mmol) in PhMe (14 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 50% EtOAc-hexane, gave **49.3** (179 mg, 68%) as a crystalline solid: FTIR (acetone cast) 3194, 2867, 1771, 1660 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 3.65 (dd, J = 11.3, 3.48 Hz, 1 H), 3.78 (dd, J = 9.1, 7.35 Hz, 1 H), 3.91 (td, J = 7.15, 1.71 Hz, 1 H), 4.09 (t, J = 11.4 Hz, 2 H), 5.30 (q, J = 3.5 Hz, 1 H), 11.75-12.25 (br s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 42.06 (d'), 71.7 (t'), 73.9 (t'), 82.2 (d'), 150.7 (s'), 165.6 (s'); exact mass m/z calcd for $C_6H_7NO_4$ 157.0375, found 157.0372.

The oxime geometry was not determined.

3,6-Anhydro-5,7,8-tris-*O*-(phenylmethyl)-L-glycero-D-ido-2-octulosonic Acid γ-Lactone 2-Oxime (50.1).



46.12 **50.1**

The general procedure for radical cyclization was followed, using **46.12** (328.3 mg, 0.3639 mmol) in PhMe (22 mL), Bu_3SnH (318 mg, 1.09 mmol) in PhMe (10 mL), and AIBN (27 mg, 0.16 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 30% EtOAc-hexane, gave **50.1** (110.4 mg, 61%) as a foam: FTIR (CH_2Cl_2 cast) 3237, 3063, 3030, 2869, 1784 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 3.68 (dd, *J* = 10.9, 4.6 Hz, 1 H), 3.88 (dd, *J* = 10.9, 1.8 Hz, 1 H), 4.02-4.15 (m, 2 H), 4.39 (d, *J* = 2.9 Hz, 1 H), 4.44-4.62 (m, 4 H), 4.69 (d, *J* = 11.5 Hz, 1 H), 4.78 (d, *J* = 11.5 Hz, 1 H), 5.01 (d, *J* = 5.4 Hz, 1 H), 5.41 (d, *J* = 5.4 Hz, 1 H), 7.21-7.42 (m, 15 H), 10.42-10.79 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 70.4 (t'), 71.4 (d'), 72.6 (t'), 72.9 (t'), 73.8 (t'), 76.0 (d'), 80.2 (d'), 81.5 (d'), 82.7 (d'), 127.8 (d'), 127.9 (d'), 128.0 (d'), 128.1 (d'), 128.4 (d'), 128.6 (d'), 128.7 (d'), 128.8 (d'), 137.6 (s'), 138.7 (s'), 138.9 (s'), 146.8 (s'), 164.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{29}H_{29}NNaO_7$ (M + Na) 526.1841,

found 526.1841.

The oxime geometry was not determined.

1-Oxospiro[4.5]decan-2,3-dione 3-Oxime (50.2).

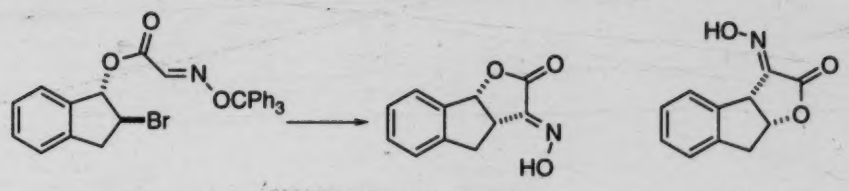
46.8 **50.2**

The general procedure for radical cyclization was followed, using **46.8** (481 mg, 0.953 mmol) in PhMe (60 mL), Bu_3SnH (694 mg, 2.38 mmol) in PhMe (12 mL), and AIBN (32 mg, 0.19 mmol) in PhMe (12 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 30% EtOAc-hexane, gave **50.2** (139.9 mg, 80%) as a crystalline solid: mp 133-135 °C; FTIR (CH_2Cl_2 cast) 3264, 2936, 2861, 1764 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.35-1.88 (m, 10 H), 2.86 (s, 2 H), 10.2 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 22.8 (t'), 24.8 (t'), 36.3 (s'), 38.2 (t'), 85.4 (t'), 149.4 (s'), 165.6 (s'); exact mass (electrospray) *m/z* calcd for $C_9H_{14}NO_3$ (M + H) 184.0973, found 184.0975.

The oxime geometry was not determined.

(3aα,8aα)-4,8b-Dihydro-2*H*-indeno[1,2-b]furan-2,3(3a*H*)-dione 3-Oxime (51.1) and (3aα,8bα)-8,8a-Dihydro-2*H*-indeno[2,1-b]furan-2,3(3a*H*)-dione 3-Oxime

(51.2).



46.6 **51.1** **51.2**

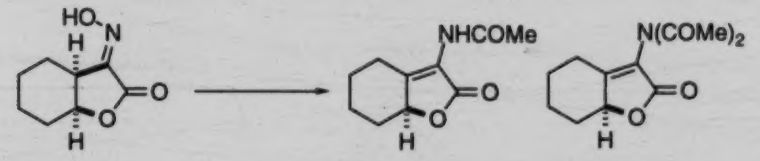
The general procedure for radical cyclization was followed, using **46.6** (700 mg, 1.33 mmol) in PhMe (83 mL), Bu_3SnH (780 mg, 2.67 mmol) in PhMe (15 mL), and AIBN (44 mg, 0.27 mmol) in PhMe (15 mL). The solvent was evaporated and the residue was covered with 30% EtOAc-hexane and let stand for 0.5 h. The precipitate was then filtered off and washed with 30% EtOAc-hexane (2 x 5 mL) to give a first crop of **51.1** (54 mg, 20%) as a crystalline solid. Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.7 x 34 cm), using 30% EtOAc-hexane, gave a 1:1 mixture (125.6 mg, 46%) of **51.1** and **51.2** as a crystalline solid.

The fraction corresponding to **51.1** had: mp 199-201 °C; FTIR (CH_2Cl_2 cast) 3189, 2856, 1765 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 3.20 (dd, J = 17.4, 4.3 Hz, 1 H), 3.58 (dd, J = 17.4, 10.2 Hz, 1 H), 4.12-4.21 (m, 1 H), 6.11 (d, J = 7.7 Hz, 1 H), 7.28-7.41 (m, 3 H), 7.50-7.58 (m, 1 H), 11.9 (s, 1 H). ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 35.9 (t'), 39.2 (d'), 85.9 (d'), 126.0 (d'), 127.0 (d'), 128.2 (d'), 130.9 (d'), 139.9 (d'), 139.7 (s'), 144.2 (s'), 152.1 (s'), 165.7 (s'); exact mass m/z calcd. for $C_{11}H_9NO_3$ 203.0582, found 203.0579. The

oxime geometry was not determined.

The mixture of **51.1** and **51.2** had: FTIR (CH_2Cl_2 cast) 3191, 2857, 1766 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 3.14-3.34 (m, 1 H), 3.41-3.65 (m, 1 H), 4.11-4.23 (m, 0.4 H), 5.06 (d, *J* = 5.8 Hz, 0.5 H), 5.45 (t, *J* = 5.7 Hz, 0.6 H), 6.10 (d, *J* = 7.7 Hz, 0.4 H), 7.16-7.67 (m, 4 H), 11.95 (s, 1 H); ^{13}C NMR (acetone-d_6, 100.6 MHz) δ 35.9 (t'), 39.2 (d'), 39.4 (t'), 48.7 (d'), 82.3 (d'), 85.9 (d'), 126.0 (d'), 126.1 (d'), 127.1 (d'), 127.2 (d'), 128.2 (d'), 128.5 (d'), 129.3 (d'), 130.9 (d'), 139.7 (s'), 140.1 (s'), 141.4 (s'), 144.1 (s'), 149.9 (s'), 152.0 (s'), 165.4 (s'), 165.7 (s'); exact mass *m/z* calcd. for $C_{11}H_9NO_3$ 203.0582, found 203.0581. The oxime geometry for **51.2** was not determined.

***N*-(2,4,5,6,7,7a-Hexahydro-2-oxo-3-benzofuranyl)-acetamide (53.1) and *N*-Acetyl-*N*-(2,4,5,6,7,7a-hexahydro-2-oxo-3-benzofuranyl)acetamide (53.2).**



49.1 **53.1** **53.2**

Ac_2O (0.52 mL) was added to a stirred a solution of oxime **49.1** (116 mg, 0.686 mmol) in DMF (2 mL), followed by iron powder (0.35 g, 6.2 mmol), and the reaction was initiated by adding a few drops of Me_3SiCl (N_2 atmosphere).

Stirring was continued for 14 h. The mixture was diluted with Et_2O and the resulting solid was filtered off through a short column of Celite (ca 1 cm thick). Evaporation of the filtrate and flash chromatography over silica gel (1.7 x 34 cm), using 1:1 EtOAc-hexane, gave **53.1** (73 mg, 54%) as a crystalline solid and **53.2** (47.3 mg, 30%) as a colorless oil.

Compound **53.1** had: mp 117-118 °C; FTIR (CH_2Cl_2 cast) 3278, 2942, 2862, 1753, 1703, 1673 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.17-1.55 (m, 3 H), 1.82-1.99 (m, 2 H), 2.10 (s, 3 H), 2.19 (dt, *J* = 13.7, 5.5 Hz, 1 H), 2.44-2.58 (m, 1 H), 3.15 (d, *J* = 14.6 Hz, 1 H), 4.67 (dd, *J* = 11.3, 6.0 Hz, 1 H), 7.58-7.79 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 22.9 (t'), 23.6 (q'), 26.3 (t'), 28.4 (t'), 34.5 (t'), 80.3 (d'), 117.9 (s'), 151.6 (s'), 168.3 (s'), 170.9 (s'); exact mass *m/z* calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0893.

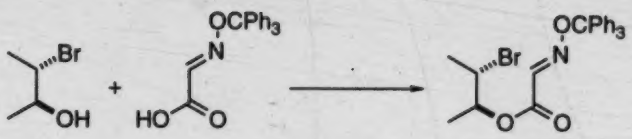
Compound **53.2** had: FTIR (CH_2Cl_2 cast) 2945, 2865, 1759, 1722, 1687 cm^{-1}, ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.23-1.58 (m, 3 H), 1.88-2.05 (m, 2 H), 2.19 (dt, *J* = 13.4, 6.0 Hz, 1 H), 2.22-2.45 (br s, 6 H), 2.56-2.72 (m, 2 H), 4.85 (dd, *J* = 11.07, 6.3 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 22.7 (t'), 25.8 (t'), 26.0 (q'), 26.4 (t'), 34.6 (t'), 79.7 (d'), 122.1 (s'), 166.5 (s'), 169.3 (s'), 171.6 (s'); exact mass *m/z* calcd for $C_{12}H_{15}NO_4$ 237.1001, found 237.0996.

***N*-(2-Oxo-1-oxaspiro[4.5]dec-3-en-3-yl)acetamide (53.3).**

50.2 **53.3**

Ac_2O (0.13 mL) was added to a stirred a solution of oxime **50.2** (30.5 mg, 0.166 mmol) in DMF (0.8 mL), followed by iron powder (0.086 g, 1.5 mmol), and the reaction was initiated by adding a few drops of Me_3SiCl (N_2 atmosphere). Stirring was continued for 14 h. The mixture was diluted with Et_2O and the resulting solid was filtered off through a short column of Celite (ca 1 cm thick). Evaporation of the filtrate and flash chromatography of the residue over silica gel, using 40% EtOAc-hexane, gave **53.3** (28.4 mg, 80%) as a crystalline solid: FTIR (CD_2Cl_2 cast) 3323, 3138, 3053, 2930, 2860, 2849, 1750, 1694, 1655 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.31-1.44 (br s, 1 H), 1.57-1.78 (m, 9 H), 2.13 (s, 3 H), 7.45 (s, 1 H), 7.58-7.71 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 23.1 (t'), 23.8 (q'), 24.9 (t'), 35.7 (t'), 87.8 (s'), 125.0 (s'), 134.1 (d'), 169.1 (s'), 169.3 (s'); exact mass (*m/z*) calcd for $C_{11}H_{15}NO_3$ 209.1052, found 209.1049.

rel-(1*R*,2*R*)-2-Bromo-1-methylpropyl [(Triphenylmethoxy)imino]acetate (54.2).

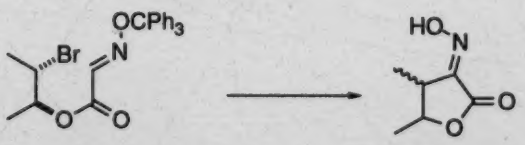


54.1 **45.3** **54.2**

The general procedure for coupling alcohols with **45.3** was followed, using **45.3** (427 mg, 1.29 mmol), DCC (300 mg, 1.42 mmol), DMAP (16 mg, 0.13 mmol), and alcohol **54.1**[59] (215.4 mg, 1.417 mmol) in CH_2Cl_2 (10 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 5% EtOAc-hexane, gave **54.2** (502.5 mg, 84%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3087, 3058, 1742, 1723 cm^{-1}; ^1H NMR (CD_2Cl_2, 200 MHz) δ 1.47 (d, J = 6.3 Hz, 3 H), δ 1.73 (d, J = 6.8 Hz, 3 H), 4.23-4.39 (m, 1 H), 5.07-5.24 (m, 1 H), 7.38-7.55 (m, 15 H), 7.9 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 18.6 (q'), 23.3 (q'), 53.3 (d'), 76.5 (d'), 95.2 (s'), 129.7 (d'), 129.9 (d'), 131.3 (d'), 143.5 (d'), 145.5 (s'), 162.8 (s'); exact mass (m/z) calcd for $C_{25}H_{24}{}^{79}BrNO_3$ 465.0939, found 465.0933.

The oxime geometry was not determined.

cis- and trans-(3*E*)-Dihydro-4,5-dimethyl-2,3-furandione Oxime (54.3).



54.2 **54.3**

The general procedure for radical cyclization was followed, using **54.2** (864.7 mg, 1.859 mmol) in PhMe (120 mL), Bu_3SnH (812 mg, 2.79 mmol) in PhMe (16 mL), and AIBN (31 mg, 0.19 mmol) in PhMe (16 mL). Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 20% EtOAc-hexane, gave **54.3** (181 mg, 68%) as a crystalline mixture of isomers: mp 101-102 °C; FTIR (CH_2Cl_2 cast) 3211, 2982, 2937, 2874, 1766 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.21 (d, J = 7.4, 1 H), δ 1.37-1.43 (m, 5 H), 2.98-3.10 (m, 0.5 H) 3.51 (quintet, J = 7.2 Hz, 0.4 H), 4.34-4.42 (m, 0.5 H), 4.78 (quintet, J = 6.6 Hz, 0.4 H), 10.04-11.2 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 10.0 (q'), 14.9 (q'), 15.7 (q'), 21.5 (q'), 35.4 (d'), 39.5 (d'), 78.1 (d'), 82.4 (d'), 151.9 (s'), 153.3 (s'), 166.1 (s'); exact mass m/z calcd for $C_6H_9NO_3$ 143.0582, found 143.0580.

X-Ray analysis established that the crystal was a 55:45 mixture of trans,*E* and cis,*E* isomers.

***N*-(2,5-Dihydro-4,5-dimethyl-2-oxo-3-furanyl)-2,2,2-trifluoroacetamide (54.4).**

54.3 **54.4**

$(CF_3CO)_2O$ (592 mg, 2.82 mmol), was added to a stirred a solution of oxime **54.3** (70.6 mg, 0.494 mmol) in DMF (1.3 mL),

followed by iron powder (250 mg, 4.46 mmol), and the reaction was initiated by adding a few drops of Me_3SiCl (N_2 atmosphere). Stirring was continued for 22 h. The mixture was diluted with Et_2O and the resulting solid was filtered off through a short column of Celite (ca 1 cm thick). Evaporation of the filtrate and flash chromatography of the residue over silica gel (1.7 x 34 cm), using 25% EtOAc-hexane, gave **54.4** (88 mg, 79%) as a light yellow oil: FTIR (CH_2Cl_2 cast) 3264, 3070, 2936, 1733 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.51 (d, J = 6.7 Hz, 3 H), 2.11 (s, 3 H), 5.01 (q, J = 6.7 Hz, 1 H), 8.58-8.81 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 13.5 (q'), 18.2 (q'), 80.3 (d'), 115.9 (quaternary **C** signal split into q, J = 290 Hz), 119.6 (s'), 155.2 (s', signal split into q, J = 38.0 Hz), 156.7 (s'), 169.8 (s'); exact mass (m/z) calcd for $C_8H_8F_3NO_3$ 223.0456, found 223.0455.

3-Amino-4,5-dimethyl-2(5*H*)-furanone (54.5).

54.4 **54.5**

K_2CO_3 (40%$^w/_v$, 10 mL) in 1:1 MeOH-water was added to compound **54.4** (193 mg, 0.865 mmol) and the mixture was stirred overnight at 50 °C. The MeOH was evaporated and the resulting aqueous solution was extracted with Et_2O (2 x 10 mL). The combined ether extracts were dried ($MgSO_4$) and

evaporated. Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 30% EtOAc-hexane, gave **54.5**[46] (45.1 mg, 41%) as a crystalline solid: mp 79-81 °C, FTIR (CH_2Cl_2 cast) 3442, 3354, 3205, 2991, 2914, 1729, 1689 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 1.34 (d, *J* = 6.6 Hz, 3 H), 1.81 (d, *J* = 1.3 Hz, 3 H); 3.23-3.49 (br s, 2 H), 4.73-4.82 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 9.9 (q'), 18.8 (q'), 78.9 (d'), 128.4 (s'), 129.3 (s'), 170.9 (s'); exact mass *m/z* $C_6H_9NO_2$ 127.0633, found 127.0632.

General procedure for coupling of *O*-(Triphenylmethyl)hydroxylamine 45.1 with aldehydes.

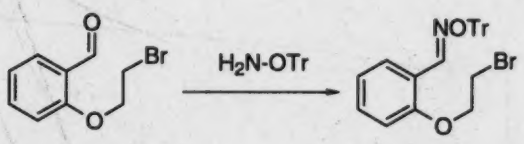
O-(Triphenylmethyl)hydroxylamine **45.1** (1.0 equiv.) was added to a stirred solution of aldehyde (1.0 equiv.) in dry THF. The reaction flask was then equipped with a reflux condenser sealed with a rubber septum, and the mixture was heated to 65 °C for 12 h, cooled and evaporated to give a residue which was processed as described for the individual experiments.

General procedure for Radical Cyclization.

The substrate was placed in a round-bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser sealed with a rubber septum. The system was flushed with argon, and dry solvent was injected into the flask. The solution was heated to reflux, and solutions of Bu_3SnH and the initiator in the corresponding solvent were

injected simultaneously by syringe pump over 10 h. Refluxing was continued for an arbitrary period of 2 h. The reaction mixture was cooled, and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

2-(2-Bromoethoxy)benzaldehyde *O*-(Triphenylmethyl)oxime (56.2).



56.1 **56.2**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (180 mg, 0.654 mmol) and **56.1**[60] (150 mg, 0.654 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 5% EtOAc-hexane, gave **56.2** (289 mg, 92%) as a foam: FTIR (CH_2Cl_2 cast) 3056, 3033, 1599, 1488, 1448, 1421 cm^{-1}; ^1H NMR $CDCl_3$, 200 MHz) δ 3.66 (t, J = 9.0 Hz, 2 H), 4.31 (t, J = 9.0 Hz, 2 H), 6.81-7.59 (m, 19 H), 8.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.9 (t'), 68.3 (t'), 91.1 (s'), 112.3 (d'), 121.5 (d'), 121.9 (s'), 127.1 (d'), 127.3 (d'), 127.5 (d'), 127.9 (d'), 129.3 (d'), 130.7 (d'), 144.3 (d'), 144.5 (s'), 155.9 (s'); exact mass (electrospray) m/z calcd for $C_{28}H_{24}{}^{79}BrNNaO$ (M + Na) 508.0888, found 508.08828.

The oxime geometry was not determined.

2-[(Phenylseleno)methoxy]benzaldehyde *O*-(Triphenylmethyl)oxime (56.4).

56.3 **56.4**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (193 mg, 0.702 mmol) and **56.3**[61] (204.6 mg, 0.7007 mmol) in THF (5 mL). Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 7% EtOAc-hexane, gave **56.4** (362 mg, 95%) as a foam: FTIR (CH_2Cl_2 cast) 3056, 3032, 1599, 1577, 1484, 1448 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.66 (s, 2 H), 6.82-6.91 (m, 2 H), 7.20-7.63 (m, 22 H), 8.52 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 68.7 (t'), 91.1 (s'), 114.2 (d'), 122.3 (d'), 123.2 (s'), 127.1 (d'), 127.5 (d'), 127.9 (d'), 129.4 (d'), 129.5 (s'), 130.5 (d'), 133.8 (d'), 144.4 (d'), 144.6 (s'), 154.8 (s'); exact mass (electrospray) *m/z* calcd for $C_{33}H_{27}NNaO_2{}^{80}Se$ (M + Na) 572.1104, found 572.1100.

The oxime geometry was not determined.

2-(2-Bromoethyl)benzaldehyde *O*-(Triphenylmethyl)-oxime (56.6).

56.5 **56.6**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (1.094 g, 3.978 mmol) and **56.5**[62] (1.06 g, 4.97 mmol) in THF (15 mL). Flash chromatography of the residue over silica gel (4 x 32 cm), using 5% EtOAc-hexane, gave **56.6** (1.75 g, 94%) as a foam: FTIR (CH_2Cl_2 cast) 3057, 3022, 1957, 1597, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.01-3.18 (m, 4 H), 7.11-7.45 (m, 19 H), 8.41 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 32.9 (t'), 37.5 (t'), 91.3 (s'), 127.1 (d'), 127.2 (d'), 127.5 (d'), 127.8 (d'), 129.1 (d'), 129.2 (d'), 130.4 (s'), 130.5 (d'), 131.5 (d'), 137.4 (s'), 144.3 (s'), 149.1 (d'); exact mass (electrospray) *m/z* calcd for $C_{28}H_{24}{}^{79}BrNNaO$ (M + Na) 492.0938 found 492.0928.

The oxime geometry was not determined.

5-Bromopentanal *O*-(Triphenylmethyl)oxime (56.8).

56.7 **56.8**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (850 mg, 3.08 mmol) and **56.7**[63] (505 mg, 3.08 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 5% EtOAc-hexane, gave **56.8** (1.07 g, 82%) as a foam. The material was a mixture of *Z* and *E* isomers (^{13}C NMR): FTIR (CH_2Cl_2 cast) 3056, 3022, 2935, 1596, 1491 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.43-1.54 (m, 1 H), 1.60-1.71 (m, 2 H), 1.81-1.93 (m, 1 H), 2.11-2.15 (m, 1 H), 2.53-2.6 (m, 1 H), 3.22 (t, *J* = 6.7 Hz, 1 H), 3.38 (t, *J* = 6.7 Hz, 1 H), 6.71 (t, *J* = 6 Hz, 0.42 H), 7.49-7.34 (m, 15 H), 7.52 (t, *J* = 6 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) 24.7 (t'), 24.8 (t'), 25.5 (t'), 28.5 (t'), 31.4 (t'), 32.3 (t'), 33.2 (t'), 33.4 (t'), 90.3 (s'), 90.4 (s'), 126.4 (d'), 126.9 (d'), 126.91 (d'), 127.02 (d'), 127.3 (d'), 127.35 (d'), 127.4 (d'), 127.5 (d'), 127.6 (d'), 128.8 (d'), 129.01 (d'), 129.05 (d'), 129.1 (d'), 129.2 (d'), 142.9 (s'), 144.4 (s'), 144.44 (s'), 144.5 (s'), 150.1 (d'), 151.2 (d'); exact mass *m/z* calcd for $C_{24}H_{24}{}^{79}BrNNaO$ (M + Na) 444.0938, found 444.0943.

2,3-*O*-(1-Methylethylidene)-D-ribose *O*-(Triphenylmethyl)oxime (57.2).

57.1 **57.2**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (475.1 mg, 1.723 mmol) and **57.1**[64] (298.4 mg, 1.571 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 40% EtOAc-hexane, gave **57.2** (604 mg, 86%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3438, 3057, 3033, 2986, 2934, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.33 (s, 3 H), 1.41 (s, 3 H), 1.63-2.01 (br s, 2 H), 3.31-3.72 (m, 3 H), 3.97-4.02 (m, 0.86 H), 4.33-4.41 (m, 0.32 H), 4.64 (t, *J* = 7 Hz, 0.76 H), 5.45 (t, *J* = 7 Hz, 0.27 H), 6.92 (d, *J* = 6.4 Hz, 0.26 H), 7.18-7.38 (m, 15 H),7.62 (d, *J* = 6.4 Hz, 0.73 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 25.4 (q'), 25.6 (q'), 27.6 (q'), 27.8 (q'), 64.0 (t'), 64.2 (t'), 69.6 (d'), 70.4 (d'), 72.2 (d'), 75.3 (d'), 78.4 (d'), 79.1 (d'), 91.3 (s'), 92.5 (s'), 110.1 (s'), 110.5 (s'), 127.2 (d'), 127.21 (d'), 127.5 (d'), 127.6 (d'), 127.7 (d'), 127.71 (d'), 127.8 (d'), 128.83 (d'), 128.9 (d'), 128.93 (d'), 129.6 (d'), 143.4 (s'), 143.8 (s'), 150.5 (d'), 150.7 (d'); exact mass (electrospray) *m/z* calcd for $C_{27}H_{29}NNaO_5$ (M + Na) 470.1943, found 470.1942.

5-Bromo-5-deoxy-2,3-*O*-(1-methylethylidene)-D-ribose *O*-(Triphenylmethyl)oxime (57.3).

57.2 **57.3**

Ph_3P (3.1 g, 11.7 mmol) was added to a stirred and cooled (ice-water) solution of **57.2** (2.6 g, 5.9 mmol) in pyridine (30 mL), and then CBr_4 (2.14 g, 6.45 mmol) was added in several portions at the same temperature. After the addition, the mixture was heated to 65 °C for 2 h, cooled, and diluted MeOH (10 mL). Evaporation of the solvents, and flash chromatography of the residue over silica gel (4 x 32 cm), using 10% EtOAc-hexane, gave **57.3** (2.65 g, 89%) as a foam. The material was a single isomer, but the oxime geometry was not determined: FTIR (CH_2Cl_2 cast) 3564, 3087, 3057, 3033, 2987, 2934, 1595, 1491 cm^{-1}; ^1H NMR ($CDCl_3$; 200 MHz) δ 1.30 (s, 3 H), 1.42 (s, 3 H), 1.92 (d, J = 6 Hz, 1 H), 3.33-3.61 (m, 3 H), 3.93-4.09 (m, 1 H), 4.72 (t, J = 6 Hz, 1 H), 7.21-7.51 (m, 15 H), 7.60 (d, J = 9.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 25.5 (q'), 27.7 (q'), 36.8 (t'), 68.8 (d'), 75.1 (d'), 79.1 (d'), 91.2 (s'), 110.5 (s'), 127.3 (d'), 127.8 (d'), 128.9 (d'), 143.9 (s'), 149.8 (d'); exact mass (electrospray) m/z calcd for $C_{27}H_{28}{}^{79}BrNNaO_4$ (M + Na) 532.1099, found 532.1100.

4-*O*-Acetyl-5-bromo-5-deoxy-2,3-*O*-(1-methylethylidene)-D-ribose *O*-(Triphenylmethyl)oxime (57.4).

57.3 **57.4**

Ac_2O (0.1 mL, 1 mmol) was added to a stirred solution of **57.3** (265.4 mg, 0.5214 mmol) in pyridine (1.0 mL), and stirring was continued overnight. Water (10 mL) was added and the solution was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), water (2 x 10 mL) and brine (2 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 5% EtOAc-hexane, gave **57.4** (270 mg, 96%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3057, 3034, 2987, 1749, 1491 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.31 and 1.40 (two singlets, 3 H in all), 1.43 and 1.49 (two singlets, 3 H in all), 1.59 and 1.78 (two singlets, 3 H in all), 3.44-3.58 (m, 2 H), 4.31-4.39 (m, 0.84 H), 4.61-4.72 (m, 1 H), 4.88-4.99 (m, 1 H), 5.46-5.51 (m, 0.22 H), 6.83 (d, J = 5.0 Hz, 0.69 H), 7.17-7.35 (m, 15 H), 7.42 (d, J = 8.0 Hz, 0.86 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 20.4 (q'), 20.5 (q'), 25.3 (q'), 25.4 (q'), 27.7 (q') 32.1 (t'), 32.3 (t'), 69.1 (d'), 69.7 (d'), 71.1 (d'), 74.7 (d'), 76.02 (d'), 76.06 (d'), 91.1

(s'), 91.9 (s'), 109.8 (s'), 110.0 (s'), 127.1 (d'), 127.3 (d'), 127.53 (d'), 127.56 (d'), 127.6 (d'), 127.8 (d'), 129.14 (d'), 129.18 (d'), 129.19 (d'), 129.2 (d'), 143.7 (s'), 143.9 (s'), 146.5 (d'), 146.9 (d'), 169.5 (s'), 169.7 (s'); exact mass (electrospray) *m/z* calcd for $C_{29}H_{30}{}^{79}BrNNaO_5$ (M + Na) 574.1205, found 574.1202.

D-Ribose *O*-(Triphenylmethyl)oxime (58.2).

58.1 **58.2**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (1.06 g, 3.86 mmol) and **58.1** (580 mg, 3.86 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 80% EtOAc-hexane, gave **58.2** (1.438 g, 91%) as a foam. The material was used directly, without characterization.

5-*O*-[(4-Methylphenyl)sulfonyl]-D-ribose *O*-(Triphenylmethyl)oxime (58.3).

58.2 **58.3**

TsCl (460 mg, 2.41 mmol) was added to a stirred and cooled (0 °C) solution of **58.2** (890 mg, 2.19 mmol) in pyridine (5 mL), and stirring was continued overnight. Water (10 mL) was added to quench the reaction, and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 50% EtOAc-hexane, gave **58.3** (658 mg, 54%) as a foam. The material was used directly, without characterization.

2,3,4-Tris-*O*-Acetyl-5-*O*-[(4-methylphenyl)-sulfonyl]-D-ribose *O*-(Triphenylmethyl)oxime (58.4).

58.3 **58.4**

Pyridine (4.6 mL, 80 mmol) was added to a stirred and cooled (0 °C) solution of **58.3** (405 mg, 0.722 mmol) in Ac_2O (10.6 mL, 144 mmol), and stirring was continued overnight. Water (15 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$. The organic extract was washed with water (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 20% EtOAc-hexane, gave **58.4** (459 mg, 93%) as a foam. The material, which was used with only partial

characterization (^{1}H NMR), appeared to be a single isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.86 (s, 3 H), 1.91 (s, 5 H), 2.2 (s, 1 H), 2.4 (s, 3 H), 4.01-4.3 (m, 2 H), 4.94-5.09 (m, 1 H), 5.22-5.48 (m, 2 H), 7.18-7.42 (m, 17 H), 7.49 (d, J = 7 Hz, 1 H), 7.66-7.81 (m, 2 H).

The oxime geometry was not determined.

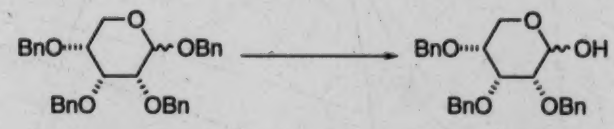
2,3,4-Tris-*O*-Acetyl-5-Bromo-5-deoxy-D-ribose *O*-(Triphenylmethyl)oxime (58.5).

58.4 **58.5**

DMF (10 mL) was added to a stirred mixture of LiBr (dried at 100 °C, 140 mg, 1.55 mmol) and **58.4** (266 mg, 0.387 mmol). The solution was stirred for 8 h, Et_2O (20 mL) was added, and the mixture was washed with water (4 x 10 mL). The ether extract was washed with water (2 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 15% EtOAc-hexane, gave **58.5** (198 mg, 86%) as a foam. The material, which was used with only partial characterization (^{1}H NMR), appeared to be a single isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88-2.2 (two singlets, 9 H), 3.24-3.58 (m, 2 H), 5.01-5.16 (m, 1 H), 5.34-5.46 (m, 1 H), 5.48-5.51 (m, 1 H), 7.01-7.49 (m, 15 H), 7.52 (d, J = 7 Hz, 1 H).

The oxime geometry was not determined.

2,3,4-Tris-*O*-(phenylmethyl)-D-ribopyranose (59.2).[65]



59.1 **59.2**

Hydrochloric acid (1 N, 1.5 mL) was added to a stirred solution of **59.1**[65] (770 mg, 1.51 mmol) in AcOH (10 mL) and the mixture was heated to 80 °C for 6 h, cooled, quenched by addition of saturated aqueous $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (15 mL), and washed with saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL). The organic extract was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using first 20% EtOAc-hexane (100 mL) and then 40% EtOAc-hexane (200 mL), gave lactols **59.2** (388 mg, 61%) as a crystalline solid: ^1H NMR ($CDCl_3$, 500 MHz) δ 3.04-3.12 (m, 0.44 H), 3.16 (dd, J = 7.5, 2.4 Hz, 0.5 H), 3.34 (t, J = 3 Hz, 0.6 H), 3.44-3.57 (m, 1 H), 3.66 (dd, J = 11.0, 5.1 Hz, 0.6 H), 3.76-3.93 (m, 1 H), 4.01 (t, J = 11.0 Hz, 0.7 H), 4.23 (s, 0.6 H), 4.48-4.91 (m, 6 H), 5.09-5.15 (m, 1 H), 5.45 (dd, J = 10.2, 1.1 Hz, 0.53 H), 7.13-7.51 (m, 15 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 56.2 (t'), 62.4 (t'), 70.6 (t'), 71.3 (t'), 71.4 (t'), 72.4 (t'), 74.0 (t'), 74.4 (d'), 74.6 (d'), 74.7 (d'), 75.2 (t'), 75.3 (d'), 76.8 (d'), 79.5

(d'), 91.9 (s'), 94.7 (s'), 127.31 (d'), 127.36 (d'), 127.4 (d'), 127.5 (d'), 127.63 (d'), 127.68 (d'), 127.7 (d'), 127.81 (d'), 127.85 (d'), 127.87 (d'), 128.0 (d'), 128.1 (d'), 128.3 (d'), 128.31 (d'), 128.4 (d'), 128.41 (d'), 128.43 (d'), 137.6 (s'), 137.7 (s'), 137.8 (s'), 137.9 (s'), 138.2 (s'), 138.8 (s').

2,3,4-Tris-*O*-(phenylmethyl)-D-ribose *O*-(Triphenylmethyl)oxime (59.3).

59.2 **59.3**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (80 mg, 0.29 mmol) and **59.2** (110 mg, 0.26 mmol) in THF (5 mL). Flash chromatography of the residue over silica gel (1.7 x 25 cm), using 15% EtOAc-hexane, gave **59.3** (167 mg, 94%) as a foam. The material was a mixture of *Z* and *E* isomers (^{1}H NMR): FTIR (CH_2Cl_2 cast) 3462, 3060, 2869, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.24-3.31 (m, 1 H), 3.60-3.78 (m, 2.3 H), 3.85 (dd, *J* = 7.0, 2.8 Hz, 0.93 H), 3.95 (dd, *J* = 7.0, 2.8 Hz, 0.25 H), 4.01-4.22 (m, 3.6 H), 4.37-4.58 (m, 2 H), 4.62-4.89 (m, 2 H), 5.24 (dd, *J* = 6.0, 2.0 Hz, 0.2 H), 6.84 (d, *J* = 7 Hz, 0.2 H), 6.98-7.44 (m, 30 H), 7.66 (d, *J* = 7.0 Hz, 0.98 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 61.0 (t'), 70.5 (t'), 72.4 (t'), 74.5 (t'), 77.1 (d'),

78.5 (d'), 80.4 (d'), 90.8 (s'), 127.0 (d'), 127.46 (d'), 127.49 (d'), 127.53 (d'), 127.55 (d'), 127.57 (d'), 127.6 (d'), 127.7 (d'), 127.81 (d'), 127.84 (d'), 128.1 (d'), 128.21 (d'), 128.23 (d'), 128.3 (d'), 128.31 (d'), 128.34 (d'), 129.0 (d'), 129.1 (d'), 137.6 (s'), 137.7 (s'), 144.2 (s'), 148.9 (d'); exact mass *m/z* calcd for $C_{45}H_{43}NO_5$ 678.3219, found 678.3217.

The oxime geometry was not determined.

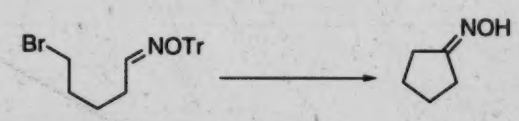
5-Bromo-5-deoxy-2,3,4-tris-*O*-(phenylmethyl)-D-ribose *O*-(Triphenylmethyl)oxime (59.4).

59.3 **59.4**

Ph_3P (90 mg, 0.34 mmol) was added to a stirred and cooled (ice-water) solution of **59.3** (115 mg, 0.169 mmol) in pyridine (5 mL), and then CBr_4 (70 mg, 0.2 mmol) was added in one portion. The mixture was then heated to 65 °C for 2 h. cooled, and diluted MeOH (5 mL). Evaporation of the solvents, and flash chromatography of the residue over silica gel (1.7 x 20 cm), using 10% EtOAc-hexane, gave **59.4** (109 mg, 86%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3060, 3030, 2866, 1958, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.34-3.43 (m, 1 H), 3.53-3.74 (m, 2 H), 3.79-4.08 (m, 2 H), 4.19-5.30 (m, 6 H), 6.88 (d, J = 7

Hz, 0.13 H), 7.22-7.46 (m, 30 H), 7.68 (d, J = 7 Hz, 0.77 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.6 (t'), 33.7 (t'), 70.7 (t'), 71.71 (d'), 71.73 (t'), 72.2 (t'), 72.5 (t'), 73.4 (t'), 74.7 (t'), 76.5 (d'), 77.1 (d'), 77.2 (d'), 79.8 (d'), 80.8 (d'), 90.8 (s'), 127.1 (d'), 127.2 (d'), 127.5 (d'), 127.6 (d'), 127.64 (d'), 127.7 (d'), 127.75 (d'), 127.81 (d'), 127.85 (d'), 127.9 (d'), 128.11 (d'), 128.17 (d'), 128.2 (d'), 128.3 (d'), 128.31 (d'), 128.35 (d'), 128.4 (d'), 129.1 (d'), 129.2 (d'), 129.3 (d'), 137.5 (s'), 137.6 (s'), 138.1 (s'), 144.1 (s'), 144.3 (s'), 149.3 (d'); exact mass m/z calcd for $C_{45}H_{42}{}^{79}BrNNaO_4$ (M + Na) 762.2194, found 762.2189.

Cyclopentanone Oxime (60.1).[66]



56.8 **60.1**

(a) Use of THF

The general procedure for radical cyclization was followed, using **56.8** (374 mg, 0.888 mmol) in THF (55 mL), Bu_3SnH (520 mg, 1.76 mmol) in THF (10 mL), and AIBN (45 mg, 0.26 mmol) in THF (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (528 mg, 1.81 mmol) and AIBN (48 mg, 0.29 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was

continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm), using 30% EtOAc-hexane, gave **60.1** (35.3 mg, 41%).

(b) Use of THF, *i*-Pr_2NEt and ABC (Best conditions)

Radical cyclization was carried out, using **56.8** (266 mg, 0.632 mmol) in THF (40 mL), Bu_3SnH (680 mg, 2.53 mmol) in THF (10 mL), ABC (16 mg, 0.06 mmol) in THF (10 mL), and *i*-Pr_2NEt (408 mg, 3.16 mmol). Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **60.1** (25.8 mg, 41%) as a crystalline solid: mp 56-58 °C; FTIR (CH_2Cl_2 cast) 3237, 2961, 2872, 1688, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.67-1.82 (m, 4 H), 2.24-2.39 (m, 2 H), 2.4-2.58 (m, 2 H), 7.5-8.8 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 24.7 (t'), 25.3 (t'), 27.1 (t'), 30.9 (t'), 167.3 (s'); exact mass *m/z* calcd for C_5H_9NO 99.0684, found 99.0681.

2,3-Dihydro-4*H*-1-benzopyran-4-one Oxime (61.1).

56.2 **61.1**

(a) Use of PhMe

The general procedure for radical cyclization was followed, using **56.2** (310 mg, 0.64 mmol) in PhMe (40 mL), Bu_3SnH (370 mg, 1.28 mmol) in PhMe (10 mL), and AIBN (20 mg,

0.13 mmol) in PhMe (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (373 mg, 1.28 mmol) and AIBN (20 mg, 0.13 mmol), each in PhMe (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm), using 5% EtOAc-hexane (200 mL), followed by 15% EtOAc-hexane (200 mL), gave **61.1** (44.8 mg, 43%) as a crystalline solid. See below for characterization data.

(b) Use of THF as solvent

Radical cyclization was carried out using **56.2** (202.7 mg, 0.4171 mmol) in THF (30 mL), Bu_3SnH (248.8 mg, 0.8348 mmol) in THF (10 mL), and AIBN (15 mg, 0.08 mmol) in THF (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (248 mg, 0.852 mmol) and AIBN (14.5 mg, 0.088 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (48.1 mg, 71%).

(c) Use of THF in the presence of 2-pyridone

Radical cyclization was carried out using **56.2** (255 mg, 0.524 mmol) in THF (35 mL) containing pyridone (65 mg, 0.68 mmol), Bu_3SnH (310 mg, 1.05 mmol) in THF (10 mL), and AIBN

(20 mg, 0.11 mmol) in THF (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (310.0 mg, 1.049 mmol) and AIBN (20.2 mg, 0.123 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 20 cm) gave **61.1** (60.8 mg, 71%).

(d) Use of THF in the presence of *N*-methyl pyrrolidine

Radical cyclization was carried out using **56.2** (174.4 mg, 0.3588 mmol) in THF (25 mL) containing *N*-methyl pyrrolidine (54 mg, 0.53 mmol), Bu_3SnH (205.5 mg, 0.7172 mmol) in THF (10 mL), and AIBN (18 mg, 0.16 mmol) in THF (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (205 mg, 0.704 mmol) and AIBN (18.2 mg, 0.111 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (40 mg, 69%).

(e) Use of MeCN

Radical cyclization was carried out using **56.2** (206 mg, 0.424 mmol) in MeCN (30 mL), Bu_3SnH (250 mg, 0.847 mmol) in MeCN (6 mL), and AIBN (21 mg, 0.13 mmol) in MeCN (6 mL). As a considerable amount of starting material was present after

the arbitrary reflux period (TLC control), further portions of Bu_3SnH (251 mg, 0.862 mmol) and AIBN (21.3 mg, 0.129 mmol), each in MeCN (6 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm), gave **61.1** (36.1 mg, 52%).

(f) Use of DME

Radical cyclization was carried out using **56.2** (196.9 mg, 0.4051 mmol) in DME (25 mL), Bu_3SnH (240 mg, 0.825 mmol) in DME (5 mL), and AIBN (21 mg, 0.12 mmol) in DME (5 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (243 mg, 0.834 mmol) and AIBN (21.3 mg, 0.129 mmol), each in DME (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm), gave **61.1** (44.3 mg, 67%).

(g) Presence of pyridine

Radical cyclization was carried out using **56.2** (153.2 mg, 0.3152 mmol) in THF (25 mL) containing pyridine (36 mg, 0.44 mmol), Bu_3SnH (183.5 mg, 0.6304 mmol) in THF (5 mL), and AIBN (16 mg, 0.10 mmol) in THF (5 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (183.9 mg, 0.6318 mmol) and AIBN (16 mg, 0.10 mmol), each in

THF (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave crude **61.1** (48.3 mg) as a crystalline solid which was mixed with AIBN-derived impurities. Recrystallization of the mixture from hexane gave **61.1** (27.6 mg, 54%).

(h) Presence of $Ti(OPr\text{-}i))_4$

Radical cyclization was carried out using **56.2** (157 mg, 0.323 mmol) in THF (25 mL) containing $Ti(OPr\text{-}i))_4$ (385.2 mg, 1.292 mmol), Bu_3SnH (190 mg, 0.65 mmol) in THF (5 mL), and AIBN (16 mg, 0.10 mmol) in THF (5 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (190 mg, 0.65 mmol) and AIBN (16.1 mg, 0.098 mmol), each in THF (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 15 cm) gave **61.1** (20.6 mg, 39%).

(i) Use of dioxane

Radical cyclization was carried out using **56.2** (168 mg, 0.346 mmol) in dioxane (21 mL), Bu_3SnH (205 mg, 0.691 mmol) in dioxane (5 mL), and AIBN (17 mg, 0.10 mmol) in dioxane (5 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (208 mg, 0.714 mmol) and AIBN

(17.2 mg, 0.105 mmol), each in dioxane (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (25 mg, 45%).

(j) Presence of Bu_3SnCl

Radical cyclization was carried out using **56.2** (209 mg, 0.431 mmol) in THF (25 mL) containing Bu_3SnCl (560 mg, 1.72 mmol), Bu_3SnH (240 mg, 0.861 mmol) in THF (5 mL), and AIBN (21 mg, 0.13 mmol) in THF (5 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (244 mg, 0.838 mmol) and AIBN (22 mg, 0.14 mmol), each in THF (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (47.3 mg, 68%).

(k) Use of DMSO-THF

Radical cyclization was carried out using **56.2** (164 mg, 0.337 mmol) in DMSO (20 mL), Bu_3SnH (194.7 mg, 0.6689 mmol) in 1:1 DMSO-THF (4 mL), and AIBN (17 mg, 0.10 mmol) in 1:1 DMSO-THF (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (195 mg, 0.681 mmol) and AIBN (17.7 mg, 0.109 mmol), each in 1:1 DMSO-THF (4 mL), were added slowly (10 h) as before, and refluxing was continued

for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 15 cm) gave **61.1** (23.4 mg, 43%).

(l) Use of sulfolane

Radical cyclization was carried out using **56.2** (161.2 mg, 0.3317 mmol) in THF (20 mL) containing sulfolane (80 mg, 0.66 mmol), Bu_3SnH (195 mg, 0.663 mmol) in THF (4 mL), and AIBN (16 mg, 0.10 mmol) in THF (4 mL). Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (44 mg, 81%) as a crystalline solid which was mixed with AIBN-derived impurities. Recrystallization of the mixture from hexane gave **61.1** (33 mg, 61%).

(m) Use of tetrahydropyran

Radical cyclization was carried out using **56.2** (157.4 mg, 0.3238 mmol) in tetrahydropyran (20 mL), Bu_3SnH (188.5 mg, 0.6476 mmol) in tetrahydropyran (4 mL), and AIBN (16 mg, 0.10 mmol) in THP (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (188.9 mg, 0.6491 mmol) and AIBN (16.6 mg, 0.101 mmol), each in THP (4 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (36 mg, 68%).

(n) Presence of $(Boc)_2O$

Radical cyclization was carried out using **56.2** (157 mg, 0.323 mmol) in THF (20 mL) containing $(Boc)_2O$ (80.0 mg, 0.355 mmol), Bu_3SnH (170 mg, 0.646 mmol) in THF (4 mL), and AIBN (11 mg, 0.06 mmol) in THF (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (170.8 mg, 0.5868 mmol) and AIBN (11.8 mg, 0.072 mmol), each in THF (4 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave crude **61.1** (43.8 mg, 84%) as a crystalline solid which was mixed with AIBN-derived impurities. Recrystallization of the mixture from hexane gave **61.1** (36.1 mg, 69%).

(o) Use of a relatively small amount of AIBN.

Radical cyclization was carried out using **56.2** (157 mg, 0.323 mmol) in THF (20 mL), Bu_3SnH (174 mg, 0.646 mmol) in THF (4 mL), and AIBN (1.6 mg, 0.01 mmol) in THF (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (177 mg, 0.651 mmol) and AIBN (1.67 mg, 0.099 mmol), each in THF (4 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (34.1 mg, 66%).

(p) Use of 2-butanone

Radical cyclization was carried out using **56.2** (145.4 mg, 0.2992 mmol) in 2-butanone (20 mL), Bu_3SnH (174.2 mg, 0.5985 mmol) in 2-butanone (4 mL), and AIBN (2.0 mg, 0.01 mmol) in 2-butanone (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (174.7 mg, 0.6002 mmol) and AIBN (3 mg, 0.02 mmol), each in 2-butanone (4 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (24 mg, 49%).

(q) Use of EtOAc

Radical cyclization was carried out using **56.2** (145.4 mg, 0.2992 mmol) in EtOAc (20 mL), Bu_3SnH (174.2 mg, 0.5985 mmol) in EtOAc (4 mL), and AIBN (2 mg, 0.01 mmol) in EtOAc (4 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (177 mg, 0.608 mmol) and AIBN (2.8 mg, 0.017 mmol), each in EtOAc (4 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 15 cm) gave **61.1** (18 mg, 36%).

(r) Use of pyridine and ABC

Radical cyclization was carried out using **56.2** (155 mg,

0.319 mmol) in THF (20 mL), Bu_3SnH (185 mg, 0.637 mmol) in THF (5 mL), ABC (3.2 mg, 0.013 mmol) in THF (5 mL), and pyridine (100 mg, 1.28 mmol). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (186 mg, 0.641 mmol) and AIBN (3.8 mg, 0.015 mmol), each in THF (5 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (44.8 mg, 86%).

(s) Initial use of excess of reagents

Radical cyclization was carried out using **56.2** (159.4 mg, 0.3279 mmol) in THF (20 mL), Bu_3SnH (360 mg, 1.3 mmol) in THF (5 mL), ABC (8 mg, 0.03 mmol) in THF (5 mL), and pyridine (100 mg, 1.31 mmol). Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (46 mg, 86%).

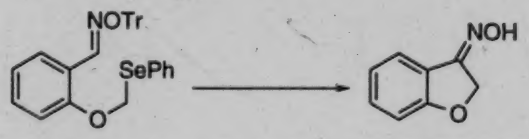
(t) Use of *i*-Pr_2NEt

Radical cyclization was carried out using **56.2** (151.7 mg, 0.3121 mmol) in THF (20 mL), Bu_3SnH (340.0 mg, 1.248 mmol) in THF (5 mL), ABC (8 mg, 0.03 mmol) in THF (5 mL), and *i*-Pr_2NEt (200 mg, 1.56 mmol). Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **61.1** (46.1 mg, 92%) as a crystalline solid: mp 139-141 °C (lit.[67] 138 °C); FTIR (CH_2Cl_2 cast) 3263, 2988, 2922, 1958, 1647 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.99 (t, J = 7.0 Hz, 2 H), 4.22 (t, J = 7.0

Hz, 2 H), 6.84-6.88 (m, 2 H), 7.21-7.26 (m, 1 H), 7.67-7.81 (m, 1 H), 8.85 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 23.6 (t'), 64.9 (t'), 117.7 (d'), 118.2 (s'), 121.4 (d'), 123.9 (d'), 131.1 (d'), 150.0 (s'), 156.6 (s'); exact mass *m/z* calcd for $C_9H_9NO_2$ 163.0633, found 163.0632.

Although the compound is known,[67] its geometry was not reported, and we did not establish the geometry.

3(2*H*)-Benzofuranone Oxime (66.1).



56.4 **66.1**

(a) Use of PhMe

The general procedure for radical cyclization was followed, using **56.4** (337 mg, 0.615 mmol) in PhMe (40 mL), Bu_3SnH (360 mg, 1.23 mmol) in PhMe (10 mL), and AIBN (30 mg, 0.2 mmol) in PhMe (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (366 mg, 1.26 mmol) and AIBN (36 mg, 0.22 mmol), each in PhMe (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm), using 15% EtOAc-hexane, gave **66.1** (44.1 mg, 48%) as a crystalline solid. See below for characterization data.

(b) Use of THF and 2-pyridone

Radical cyclization was carried out, using **56.4** (433 mg, 0.791 mmol) in THF (50 mL) containing pyridone (80 mg, 0.79 mmol), Bu_3SnH (460 mg, 1.6 mmol) in THF (10 mL), AIBN (40.0 mg, 0.237 mmol) in THF (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (466 mg, 1.61 mmol) and AIBN (44 mg, 0.27 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **66.1** (75 mg, 69%).

(c) Use of THF

Radical cyclization was carried out, using **56.4** (280 mg, 0.511 mmol) in THF (32 mL), Bu_3SnH (600 mg, 2.04 mmol) in THF (10 mL), and AIBN (8.5 mg, 0.051 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 20 cm) gave **66.1** (52.1 mg, 69%).

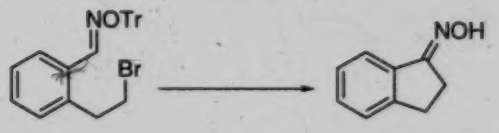
(d) Use of THF, *i*-Pr_2NEt and ABC (Best conditions)

Radical cyclization was carried out, using **56.4** (238 mg, 0.434 mmol) in THF (30 mL), Bu_3SnH (510.0 mg, 1.737 mmol) in THF (10 mL), ABC (11 mg, 0.043 mmol) in THF (10 mL), and *i*-Pr_2NEt (230 mg, 1.74 mmol). Flash chromatography of the residue over silica gel (1.7 x 20 cm) gave **66.1** (59.2 mg,

91%) as a crystalline solid: mp 158-161 °C; FTIR 3131, 3046, 2841, 1666, 1605, 1591, 1481 cm^{-1}; ^1H NMR (CD_2Cl_2, 400 MHz) δ 5.18 (s, 2 H), 6.86-7.11 (m, 2 H), 7.32-7.4 (m, 1 H), 7.58-7.60 (m, 1 H), 7.98 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 70.6 (t'), 111.4 (d'), 119.6 (s'), 121.5 (d'), 121.9 (d'), 132.7 (d'), 158.3 (s'),165.5 (s'); exact mass *m/z* calcd for $C_8H_7NO_2$ 149.0476, found 149.0477.

Although the compound is known,[68] its geometry was not reported, and we did not establish the geometry.

2,3-Dihydro-1*H*-inden-1-one Oxime (66.2).



56.6 **66.2**

(a) Use of PhMe

The general procedure for radical cyclization was followed, using **56.6** (361 mg, 0.769 mmol) in THF (50 mL), Bu_3SnH (450 mg, 1.54 mmol) in THF (10 mL), AIBN (40 mg, 0.2 mmol) in THF (10 mL), and pyridone (90 mg, 0.93 mmol). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (452 mg, 1.56 mmol) and AIBN (40 mg, 0.2 mmol), each in THF (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 20 cm),

using 15% EtOAc-hexane, gave **66.2** (74.3 mg, 67%) as a crystalline solid. See below for characterization data.

(b) Use of EtOH

Radical cyclization was carried out, using **56.6** (222 mg, 0.473 mmol) in EtOH (30 mL), Bu_3SnH (275 mg, 0.945 mmol) in EtOH (10 mL), and AIBN (24 mg, 0.14 mmol) in EtOH (10 mL). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (277 mg, 0.952 mmol) and AIBN (24.8 mg, 0.151 mmol), each in EtOH (10 mL), were added slowly (10 h) as before, and refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 20 cm) gave **66.2** (35.2 mg, 51%).

(c) Use of THF

Radical cyclization was carried out, using **56.6** (310 mg, 0.661 mmol) in the THF (41 mL), Bu_3SnH (710 mg, 2.64 mmol) in THF (10 mL), and AIBN (11 mg, 0.066 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 18 cm) gave **66.2** (65.4 mg, 67%).

(d) Use of THF, *i*-Pr_2NEt and ABC (Best conditions)

Radical cyclization was carried out, using **56.6** (211 mg, 0.449 mmol) in THF (30 mL), Bu_3SnH (524 mg, 1.81 mmol) in THF (8 mL), ABC (11 mg, 0.045 mmol) in THF (8 mL), and *i*-Pr_2NEt (232 mg, 1.81 mmol). Flash chromatography of the residue

over silica gel (1.7 x 18 cm) gave **66.2** (57.3 mg, 87%) as a crystalline solid: mp 148-150 °C (Lit.[69a] mp 153-154 °C); FTIR (CH_2Cl_2 cast) 3064, 2861, 1654, 1598, 1479, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.92-3.18 (m, 4 H), 7.20-7.41 (m, 3 H), 7.64-7.67 (m, 1 H), 9.15 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 26.0 (t'), 28.6 (t'), 121.5 (d'), 125.5 (d'), 126.9 (d'), 130.3 (d'), 135.8 (s'), 148.3 (s'), 163.9 (s'); exact mass m/z calcd for C_9H_9NO 147.0684, found 147.0682.

Although the compound is known,[69] its geometry was not reported, and we did not establish the geometry.

[4*R*-(3aα,4β,6aα)]-Tetrahydro-2,2-dimethyl-5-oximino-4*H*-cyclopenta-1,3-dioxol-4-yl Acetate (68.1).

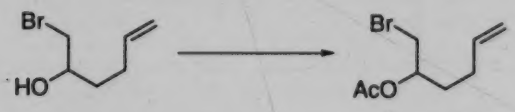
57.4 **68.1**

The general procedure for radical cyclization was followed, using **57.4** (250.0 mg, 0.4537 mmol) in THF (30 mL), Bu_3SnH (490.0 mg, 1.814 mmol) in THF (10 mL), ABC (11 mg, 0.067 mmol) in THF (10 mL), and *i*-Pr_2NEt (237.4 mg, 1.814 mmol). As some starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (141 mg, 0.484 mmol), and AIBN (8 mg, 0.5 mmol), each in THF (4 mL), were added slowly (4 h) as before, and

refluxing was continued for 2 h after the addition. Flash chromatography of the residue over silica gel (1.7 x 20 cm), using 40% EtOAc-hexane, gave **68.1** (96.0 mg, 93%) as a crystalline solid: mp 151-154 °C; FTIR 3358, 2991, 2980, 2945, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 3 H), 1.51 (s, 3 H), 2.15 (s, 3 H), 2.51-2.74 (m, 1 H), 3.11-3.32 (m, 1 H), 4.73-4.88 (m, 2 H), 7.62 (s, 1 H), δ 4.89-5.12 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 172.2 (s'), 159.6 (s'), 114.7 (s'), 80.3 (d'), 79.5 (d'), 72.0 (d'), 30.4 (t'), 28.2 (q'), 26.7 (q'), 22.5 (q'); exact mass (electrospray) *m/z* calcd for $C_{10}H_{15}NNaO_5$ (M + Na) 252.0847, found 252.0848.

The oxime geometry was not established.

(1-Bromomethyl)-4-penten-1-yl Acetate (69.2).



69.1 **69.2**

Pyridine (1 mL) was added to a stirred and cooled (0 °C) mixture of Ac_2O (5 mL) and **69.1**[70] (310 mg, 1.73 mmol), and stirring was continued overnight. Water (15 mL) was added and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, and water (1 x 10 mL), dried, and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 5% EtOAc-hexane, gave **69.2** (365 mg, 96%) as a colorless

oil: FTIR (CH_2Cl_2 cast) 3465, 3078, 2977, 2924, 1742, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.73-1.82 (m, 2 H), 2.02-2.14 (m, including a singlet at δ 2.07, 5 H in all), 3.38-3.57 (m, 2 H), 4.87-5.09 (m, 3 H), 5.70-5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 21.1 (q'), 29.4 (t'), 31.8 (t'), 34.1 (t'), 71.8 (d'), 115.5 (t'), 136.9 (d'), 170.2 (s'). A satisfactory mass spectrum could not be obtained by electron impact or electrospray methods.

(1-Bromomethyl)-4-oxobutyl Acetate (69.3).

69.2 **69.3**

OsO_4 (2.5% w/w in *t*-BuOH, 2.0 mL, 0.16 mmol) was added to a stirred mixture of **69.2** (358 mg, 1.62 mmol), water (8 mL), CCl_4 (8 mL) and *t*-BuOH (4 mL). After 20 min, the mixture had become black. $NaIO_4$ (870 mg, 4.05 mmol) was then added in one portion and the resulting mixture was stirred for 6 h. Brine (10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and aqueous $NaHSO_3$ (10%, 15 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 28 cm), using 20% EtOAc-hexane, gave **69.3** (289 mg, 80%) as a colorless oil. The material was a mixture of the aldehyde

and its hydrate: FTIR (CH_2Cl_2 cast) 3459, 2966, 2936, 1739 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.44-2.56 (m, including a singlet at δ 2.07, 7 H in all), 3.37-3.49 (m, 2 H), 4.82-5.11 (m, 2 H), 9.76 (t, J = 1.3 Hz, 0.3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.8 (q'), 20.9 (q'), 25.0 (t'), 26.4 (t'), 29.7 (t'), 33.4 t'), 33.8 (t'), 39.5 (t'), 71.5 (d'), 71.8 (d'), 100.5 (d'), 170.2 (s'), 170.3 (s'), 200.4 (d'); exact mass (electrospray) m/z calcd for $C_7H_{11}{}^{79}BrO$ (M + H) 222.9969, found 222.9967.

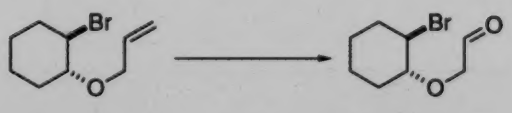
(1-Bromomethyl)-4-[(Triphenylmethoxy)imino]butyl Acetate (69.4).

69.3 **69.4**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (335 mg, 1.22 mmol) and **69.3** (272 mg, 1.22 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 10% EtOAc-hexane, gave **69.4** (571 mg, 98%) as a foam. The material was a mixture of Z and E isomers: FTIR (CH_2Cl_2 cast) 3057, 3023, 2928, 1958, 1741, 1596 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.71-1.85 (m, 1 H), 1.89-2.09 (m, 4 H), 2.11-2.31 (m, 1 H), 2.44-2.72 (m, 1 H), 3.23-3.34 (m, 1 H), 3.42-3.59 (m, 1 H), 4.78-5.10 (m, 1 H), 6.78 (t, J = 6 Hz, 0.5 H), 7.11-7.42 (m, 15

H), 7.60 (t, J = 6 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.8 (q'), 20.9 (q'), 22.2 (t'), 25.4 (t'), 28.82 (t'), 28.83 (t'), 33.3 (t'), 33.8 (t'), 71.3 (d'), 71.9 (d'), 90.4 (s'), 90.6 (s'), 126.9 (d'), 127.1 (d'), 127.2 (d'), 127.4 (d'), 127.8 (d'), 128.8 (d'), 128.9 (d'), 129.1 (d'), 144.3 (s'), 144.4 (s'), 149.3 (d'), 150.1 (d'),170.1 (s'); exact mass (electrospray) m/z calcd for $C_{26}H_{26}{}^{79}BrNNaO_3$ (M + Na) 502.0993, found 502.0993.

Trans-2-[2-Bromocyclohexyl)oxy]acetaldehyde (70.2).



70.1 **70.2**

Ozone was bubbled through a stirred and cooled (-78 °C) solution of **70.1**[71] (697.4 mg, 3.184 mmol) in CH_2Cl_2 (15 mL) for 1 h. The reaction mixture was then flushed by oxygen for 10 min, and Ph_3P (2.5 g, 9.6 mmol) was added. Stirring was continued overnight, the cold bath being left in place, but not recharged. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.7 x 30 cm), using 15% EtOAc-hexane, gave **70.2** (609 mg, 87%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3450, 2937, 2860, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19-2.42 (m, 8 H), 3.29-3.43 (m, 1 H), 3.82-4.11 (m, 1 H), 4.21 (s, 2 H), 9.79 (s, 1 H); ^{13}C

NMR ($CDCl_3$, 100.6 MHz) δ 22.9 (t'), 25.1 (t'), 30.9 (t'), 35.5 (t'), 54.8 (d'), 75.3 (t'), 83.3 (d'), 200.8 (d'); exact mass *m/z* calcd for $C_8H_{13}{}^{79}BrNaO_2$ (M + Na) 242.9996, found 242.9991.

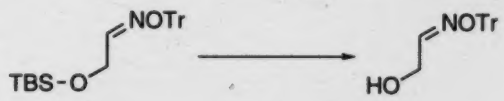
Trans-2-[2-Bromocyclohexyl)oxy]acetaldehyde *O*-(Triphenylmethyl)oxime (70.3).

70.2 **70.3**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (651 mg, 2.37 mmol) and **70.2** (523 mg, 2.36 mmol) in THF (8 mL). Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 5% EtOAc-hexane, gave **70.3** (1.06 g, 94%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3056, 3033, 2860, 1597, 1491 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.10-1.43 (m, 3 H), 1.58-2.03 (m, 4 H), 2.11-2.41 (m, 1 H), 3.11-3.23 (m, 0.6 H), 3.34-3.43 (m, 0.46 H), 3.81-4.20 (m, 2 H), 4.64 (t, *J* = 4 Hz, 1 H), 6.98 (t, *J* = 5 Hz, 0.5 H), 7.14-7.40 (m, 15 H), 7.69 (t, *J* = 5 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 23.3 (t'), 25.49 (t'), 25.5 (t'), 25.51 (t'), 31.0 (t'), 35.6 (t') 35.7 (t'), 55.1 (d'), 55.3 (d'), 64.6 (t'), 66.2 (t'), 80.7 (d'), 82.5 (d'), 90.7 (s'), 91.0 (s'), 127.0 (d'), 127.2 (d'), 127.4 (d'), 127.5 (d'), 128.8 (d'), 129.1 (d'), 129.2 (d'), 144.1 (s'), 144.2 (s'), 147.8 (d'), 151.1 (d'); exact

mass (electrospray) *m/z* calcd for $C_{27}H_{28}{}^{79}BrNNaO_2$ (M + Na) 500.1195, found 500.1199.

2-Hydroxyacetaldehyde *O*-(Triphenylmethyl)oxime (70.6).



70.5 **70.6**

Bu_4NF (1.0 M in THF, 3.4 mL, 3.4 mmol) was added dropwise to a stirred solution of **70.5**[72] (1.3 g, 3.1 mmol) in THF (10 mL). Stirring was continued for 30 min, water (15 mL) was added, and the mixture was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 35 cm), using 15% EtOAc-hexane, gave **70.6** (792 mg, 83%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3357, 3057, 1958, 1596 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.99 (br s, 1 H), 4.16-4.24 (m, 1 H), 4.58-4.63 (m, 1 H), 6.93 (t, *J* = 5.0 Hz, 0.34 H), 7.19-7.42 (m, 15 H), 7.73 (t, *J* = 5.0 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 58.2 (t'), 60.4 (t'), 90.9 (s'), 91.1 (s'), 127.2 (d'), 127.3 (d'), 127.5 (d'), 127.6 (d'), 128.8 (d'), 129.1 (d'), 144.0 (s'), 144.1 (s'), 148.7 (d'), 152.1 (d'); exact mass *m/z* calcd for $C_{21}H_{19}NNaO_2$ (M + Na) 340.1313 found, 340.1313.

Trans-2-[(2-Bromocyclohexyl)oxy]acetaldehyde *O*-(Phenylmethyl)oxime (70.7).

70.2 **70.7**

O-Benzylhydroxylamine hydrochloride (330 mg, 2.66 mmol) was added to a stirred solution of **70.2** (490 mg, 2.22 mmol) in THF (10 mL). Pyridine (350 mg, 4.44 mmol) was then added, and the mixture was refluxed for 10 h, cooled, filtered and evaporated. Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 8% EtOAc-hexane, gave **70.7** (632 mg, 88%) as light yellow oil. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3087, 3063, 2937, 2860, 1452 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19-2.4 (m, 8 H), 3.27-3.39 (m, 1 H), 3.88-3.99 (m, 1 H), 4.12-4.51 (m, 2 H), 5.09 (d, J = 1.6 Hz, 2 H), 6.87 (t, J = 4 Hz, 0.42 H), 7.23-7.59 (m, 5 H), 7.53 (t, J = 4 Hz, 0.5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.2 (t'), 25.4 (t'), 30.7 (t'), 30.9 (t'), 35.6 (t'), 54.9 (d'), 55.2 (d'), 64.0 (t'), 66.4 (t'), 75.9 (t'), 76.3 (t'), 81.5 (s'), 82.4 (s'), 127.8 (d'), 127.9 (d'), 128.0 (d'), 128.1 (d'), 128.4 (d'), 137.4 (s'), 137.5 (s'), 147.9 (d'), 151.1 (d'); exact mass *m/z* calcd for $C_{15}H_{20}{}^{79}BrNNaO_2$ (M + Na) 348.0575, found 348.0570.

The oxime geometry was not established.

(3aα,7aα)-3-[*O*-(Phenylmethoxy)imino]octahydro-benzofuran (70.8).

70.7 **70.8**

The general procedure for radical cyclization was followed, using **70.7** (281 mg, 0.865 mmol) in THF (50 mL), Bu_3SnH (370 mg, 1.30 mmol) in THF (5 mL), and ABC (4 mg, 0.02 mmol) in THF (5 mL). Flash chromatography of the residue over silica gel (1.7 x 20 cm), using 20% EtOAc-hexane, gave **70.8** (129 mg, 61%) as a foam. The material was a mixture of two isomers: FTIR (CH_2Cl_2 cast) 3242, 3086, 3062, 2931 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12-2.23 (m, 9 H), 3.41-3.46 (m, 0.68 H), 3.48-3.57 (m, 1 H), 3.91-4.20 (m, 1.8 H), 4.08-4.15 (dd, *J* = 10.3, 6.4 Hz, 0.7 H), 4.66-4.74 (two singlets, 2 H in all), 4.83-5.92 (br s, 1 H), 7.22-7.43 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.4 (t'), 20.5 (t'), 20.9 (t'), 24.1 (t'), 24.2 (t'), 26.1 (t'), 27.7 (t'), 28.2 (t'), 39.7 (d'), 41.4 (d'), 64.0 (d'), 67.1 (d'), 68.3 (t'), 69.8 (t'), 75.6 (d'), 76.0 (t'), 76.6 (t'), 77.3 (d'), 127.8 (d'), 127.9 (d'), 128.3 (d'), 128.35 (d'), 128.4 (d');137.7 (s'); exact mass *m/z* calcd for $C_{15}H_{22}NO_2$ (M + H) 248.1650, found 248.1654.

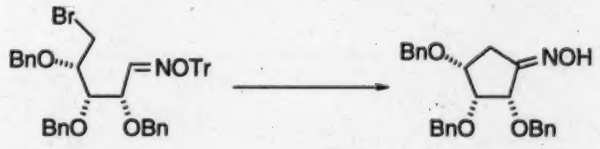
[*R*-(1α,2α,3α)-2,3-Diacetoxy-4-(oximino)cyclpentyl

Acetate (71.1).

58.5 **71.1**

The general procedure of radical cyclization was followed, using **58.5** (131 mg, 0.219 mmol) in THF (15 mL), Bu_3SnH (256 mg, 0.879 mmol) in THF (5 mL), ABC (6 mg, 0.02 mmol) in THF (5 mL), and *i*-Pr_2NEt (114 mg, 0.879 mmol). Flash chromatography of the residue over silica gel (1.7 x 20 cm), using 50% EtOAc-hexane, gave **71.1** (50.1 mg, 85%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3396, 2936, 1750, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.05 (s, 9 H), 2.73 (td, *J* = 15, 6.0 Hz, 1 H), 2.97 (dd, *J* = 15.0, 7.5 Hz, 1 H), 5.22-5.34 (m, 1.2 H), 5.49 (t, *J* = 4.5 Hz, 0.85 H), 5.68 (dd, *J* = 5.0, 2.0 Hz, 0.82 H), 6.02-6.08 (m, 0.21 H), 8.61-9.18 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.2 (q'), 20.3 (q'), 20.4 (q'), 20.5 (q'), 20.6 (q'), 20.7 (q'), 30.1 (t'), 33.0 (t'), 65.2 (d'), 68.7 (d'), 69.9 (d'), 70.0 (d'), 71.0 (d'), 71.4 (d'), 156.0 (s'), 169.7 (s'), 169.8 (s'), 170.0 (s'); exact mass *m/z* calcd for $C_{11}H_{15}NO_7$ 273.0848, found 273.0849.

[2*S*-(2α,3α,4α)]-2,3,4-Tris(phenylmethoxy)cyclopentanone Oxime (72.1).

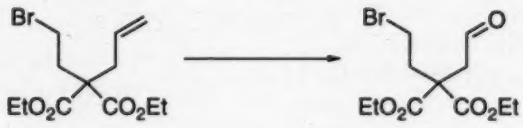


59.4 **72.1**

The general procedure for radical cyclization was followed, using **59.4** (260 mg, 0.351 mmol) in THF (25 mL), Bu_3SnH (204 mg, 0.702 mmol) in THF (5 mL), ABC (5 mg, 0.02 mmol) in THF (5 mL), and *i*-Pr_2NEt (90 mg, 0.71 mmol). As a considerable amount of starting material was present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (209 mg, 0.718 mmol) and AIBN (5.9 mg, 0.024 mmol), each in THF (5 mL), were added slowly (10 h) as before. As a considerable amount of starting material was still present after the arbitrary reflux period (TLC control), further portions of Bu_3SnH (211 mg, 0.721 mmol) and AIBN (5 mg, 0.02 mmol), each in THF (5 mL), were added slowly (10 h) as before. Flash chromatography of the residue over silica gel (1.7 x 20 cm), using 30% EtOAc-hexane, gave **72.1** (132 mg, 91%) as a crystalline solid. The material was a mixture of *Z* and *E* isomers: mp 145-147 °C; FTIR (CH_2Cl_2 cast) 3228, 3087, 3062, 2869, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.48-2.92 [m, including a doublet of doublets at δ 2.54 (J = 17, 6.3 Hz), 2 H in all], 3.76-3.97 [m, including a triplet at δ 3.8 (J = 4.6 Hz), 2 H in all], 4.16 (d, J = 4 Hz, 1 H), 4.53-4.84 (m, 6 H), 7.03-7.61 (m, 15 H), 7.78-8.87 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 30.5 (t'), 33.7 (t'), 71.41 (t'), 71.47

(t'), 71.5 (t'), 71.6 (t'), 72.5 (t'), 72.7 (t'), 73.4 (d'), 75.2 (d'), 75.3 (d'), 77.0 (d'), 78.4 (d'), 127.5 (d'), 127.53 (d'), 127.59 (d'), 127.6 (d'), 127.71 (d'), 127.75 (d'), 127.86 (d'), 127.89 (d'), 128.14 (d'), 128.16 (d'), 128.22 (d'), 128.28 (d'), 128.3 (d'), 137.8 (s'), 138.1 (s'), 138.18 (s'), 138.2 (s'), 138.21 (s'), 138.4 (s'), 158.6 (s'), 160.1 (s'); exact mass *m/z* calcd for $C_{26}H_{27}NO_4$ 417.1940, found 417.1943.

Diethyl (2-Bromoethyl)(2-oxoethyl)propanedioate (73.2).



73.1 **73.2**

OsO_4 (2.5% w/w in *t*-BuOH, 2.4 mL, 0.19 mmol) was added to a stirred mixture of **73.1**[74] (300 mg, 0.971 mmol), water (6 mL), CCl_4 (6 mL) and *t*-BuOH (3 mL). After 20 min, the mixture had become black. $NaIO_4$ (520 mg, 2.43 mmol) was then added in one portion and the resulting mixture was stirred for 6 h. Brine (10 mL) was added, and the mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with water (10 mL) and aqueous $NaHSO_3$ (10%, 15 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 10% EtOAc-hexane, gave **73.2** (251 mg, 83%) as a

colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 8 Hz, 6 H), 2.56 (t, J = 8 Hz, 2 H), 3.05 (d, J = 1.5 Hz, 2 H), 3.42 (t, J = 8 Hz, 2 H), 4.25 (q, J = 6 Hz, 4 H), 9.71 (s, 1 H).

Diethyl (2-Bromoethyl)[2-[(triphenylmethoxy)-imino]ethyl]propanedioate (73.3).

73.2 **73.3**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (260 mg, 0.943 mmol) and **73.2** (290 mg, 0.943 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 10% EtOAc-hexane, gave **73.3** (512 mg, 97%) as a foam. The material was a mixture of Z and E isomers: FTIR (CH_2Cl_2 cast) 3533, 3087, 2980, 2936, 1958, 1731, 1597 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17-1.24 (m, 6 H), 2.24 (t, J = 8.0 Hz, 1.3 H), 2.44 (t, J = 8.0 Hz, 0.7 H), 2.73-2.80 (m, 1.3 H), 3.11-3.18 (m, 2 H), 3.30-3.38 (m, 0.72 H), 4.04-4.23 (m, 4 H), 6.71 (dt, J = 5.5, 0.77 Hz, 0.36 H) 7.19-7.32 (m, 15 H), 7.50 (dt, J = 6.0, 0.6 Hz, 0.8 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 14.0 (q'), 14.1 (q'), 26.7 (t'), 26.9 (t'), 30.1 (t'), 33.2 (t'), 35.9 (t'), 37.2 (t'), 55.9 (s' or t'), 56.2 (s' or t'), 61.9 (s' or t'), 62.1 (s' or t'), 90.7 (s'), 91.1 (s'), 127.0 (d'), 127.09 (d'), 127.1 (d'), 127.2 (d'), 127.5 (d'), 127.6 (d'), 127.8 (d'),

128.9 (d'), 129.0 (d'), 144.1 (s'), 144.2 (s'), 145.9 (d'), 146.0 (d'), 169.5 (s'), 169.6 (s'); exact mass (electrospray) *m/z* calcd for $C_{30}H_{32}{}^{79}BrNNaO_5$ (M + Na) 588.1356, found 588.1361.

Diethyl (2-Iodoethyl)[2-[(triphenylmethoxy)-imino]ethyl]propanedioate (73.5).

73.3 **73.5**

Bromide **73.3** (365 mg, 0.645 mmol) was added to a stirred solution of NaI (200 mg, 1.29 mmol) in dry acetone (10 mL), and the mixture was refluxed for 24 h and cooled. Saturated aqueous $Na_2S_2O_3$ was added to the reaction mixture which was then extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with brine (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.7 x 30 cm), using 8% EtOAc-hexane, gave **73.5** (342 mg, 83%) as a foam. The material was a mixture of *Z* and *E* isomers: FTIR (CH_2Cl_2 cast) 3532, 3057, 2979, 1958, 1730, 1597 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.05-1.23 (m, 6 H), 2.31-2.98 (m, 5 H), 3.03-3.18 (m, 1 H), 4.01-4.23 (m, 4 H), 6.71 (t, *J* = 5 Hz, 0.18 H), 7.21-7.35 (m, 15 H), 7.49 (t, *J* = 5 Hz, 0.70 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ -3.0 (t'), -2.8 (t'), 13.9 (q'), 13.97 (q'), 29.7 (s' or t'), 32.9 (s' or

t'), 37.5 (s' or t'), 38.7 (s' or t'), 57.3 (s' or t'), 57.6 (s' or t'), 61.8 (s' or t'), 61.9 (s' or t'), 90.7 (s'), 91.1 (s'), 127.1 (d'), 127.20 (d'), 127.21 (d'), 127.5 (d'), 127.63 (d'), 127.68 (d'), 127.7 (d'), 127.9 (d'), 128.9 (d'), 129.1 (d'), 129.7 (d'), 144.2 (s'), 144.23 (s'), 146.0 (d'), 146.1 (d'), 146.9 (s'), 169.5 (s'),169.6 (s'); exact mass *m/z* calcd for $C_{30}H_{32}INNaO_5$ (M + Na) 636.1222, found 636.1228.

Benzaldehyde *O*-(Triphenylmethyl)oxime (75.1).

\- **75.1**

The general procedure for coupling aldehydes with **45.1** was followed, using **45.1** (500 mg, 1.82 mmol) and benzaldehyde (193 mg, 1.82 mmol) in THF (10 mL). Flash chromatography of the residue over silica gel (1.7 x 32 cm), using 5% EtOAc-hexane, gave **75.1** (521 mg, 79%) as a foam: FTIR (CH_2Cl_2 cast) 3057, 3024, 1598, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.18-7.51 (m, 20 H), 8.23 (s, 1 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 91.2 (s'), 127.0 (d'), 127.1 (d'), 127.4 (d'), 127.6 (d'), 128.4 (d'), 129.1 (d'), 129.2 (d'), 129.5 (d'), 132.6 (s'), 144.3 (s'), 148.5 (d'); exact mass *m/z* calcd for $C_{26}H_{22}NO$ (M + H) 364.1701, found 364.1708.

The oxime geometry was not established.

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75 Compound **76.1** was prepared by ozonolysis of the corresponding olefin, which was prepared by DCC-mediated coupling of allyl alcohol and 2-bromopropionic acid.

Part 3

Studies on Radical Deoxygenation

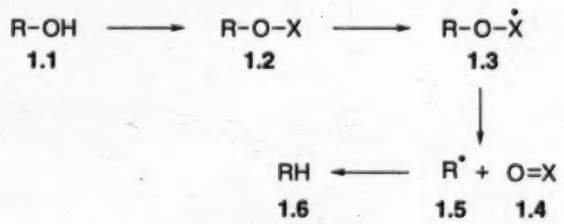
I. Introduction

Methods for the selective replacement of OH groups by H have become very important in natural product synthesis, particularly of amino glycosides and complex carbohydrates.[1] Deoxysugars are essential components of numerous biologically active natural products like cardenolides and antitumor agents.[1]

Numerous methods have been developed for the deoxygenation of alcohols.[2] Some of the conventional methods involve the reduction of suitable alcohol derivatives such as sulfate, *p*-toluenesulfonate and mesylate or the replacement of the OH group by halogen or thiolate with subsequent reductive dehalogenation or desulfurisation. These ionic reactions can be successfully used for simple, sterically unhindered molecules. However, these reactions have severe limitations in complex, polyfunctional compounds particularly with sterically hindered hydroxyl groups. The main reasons for this are that the reactants and intermediates in ionic reactions are highly solvated and thus the nucleophilic displacement reaction takes place with low efficiency due to steric hindrance and dipole repulsion. Moreover, elimination and rearrangements are common side reactions when carbocations are involved as intermediates. In carbohydrates these ionic reactions are often unsuccessful due to the opposing dipoles of neighboring β-carbon-oxygen bonds.[3]

Radical reactions offer an alternative to overcome the

limitations of ionic reactions. Radical reactions take place under neutral conditions and thus are ideally suited for application to sensitive polyfunctional compounds. Furthermore, radicals are not solvated and thus are less susceptible to the steric factors. In general, radical deoxygenation can be realized according to Scheme 1, in which a suitable alcohol derivative **1.2** is converted to an intermediate radical **1.3**, which then fragments by β-cleavage into an alkyl radical R• and a double bond species **1.4**. The alkyl radical R• then reacts with a hydrogen donor (**1.5**→**1.6**) yielding the corresponding hydrocarbon.

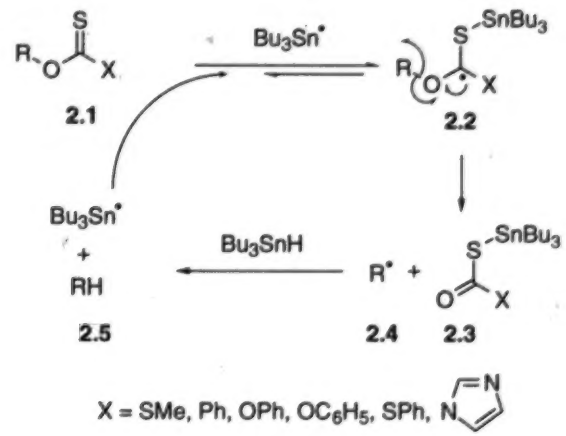


Scheme 1

A. Barton Deoxygenation and its Modifications

Barton invented the first radical deoxygenation process[4] based on the mechanism of photoelimination in *O*-alkylthiobenzoates.[5] In general, Barton deoxygenation involves the reversible addition of an organostannyl radical to a thiocarbonyl group, followed by fragmentation of the intermediate carbon-centered radical to give a carbonyl group with concomitant liberation of an alkyl radical R• (**2.4**). This radical species then reacts with the stannane to give

the corresponding hydrocarbon (Scheme 2).

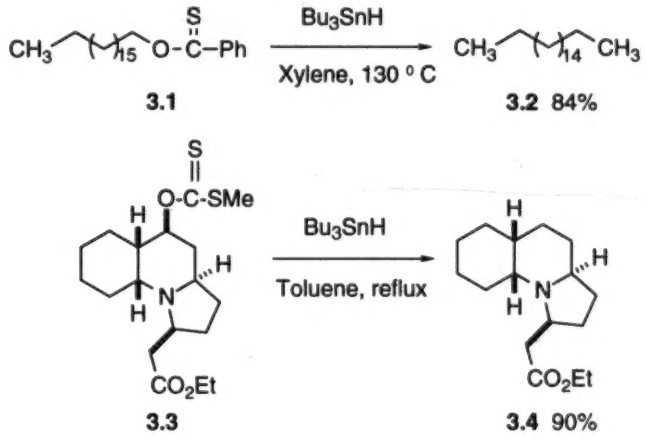


Scheme 2

The driving force for this reaction would be the energy gained by the transition from a C=S to a C=O double bond. Trialkyltin radicals are particularly suitable for these reactions as the Sn-S bond is very stable and trialkyltin hydrides are also good H-donors.

Xanthates (**2.1**, X = SMe), thiobenzoates (X = Ph) and thiocarbonyl imidazolides (X = 1-imidazolyl) are the most popular derivatives used in this process. Deoxygenations of secondary alcohols are most successful. For deoxygenation of primary alcohols higher temperatures (130-150 °C) are often required, as illustrated by comparison of the two examples in Scheme 3.[6] Tertiary alcohols can be converted into the corresponding hydrocarbons under mild conditions via thioformyl derivatives.[7] However, because of the thermal instability of many thiocarbonyl derivatives of tertiary

alcohols, the number of methods available for deoxygenation of the latter is more limited.[3]



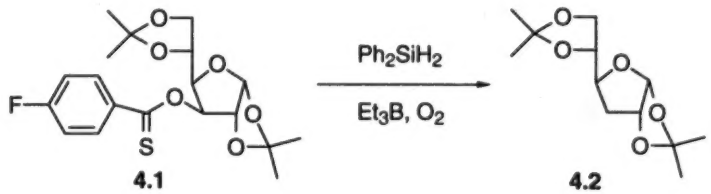
Scheme 3

Numerous applications of the Barton deoxygenation are available in the literature.[2] In this review some of the recent modifications in the reaction will be discussed.

Until recently, tributyltin hydride has played an almost exclusive role as a hydrogen atom source in the deoxygenation process. The tin-hydrogen bond is sufficiently weak and the tributyltin radical is a useful carrier of radical chain. However, it is not always easy to remove traces of toxic tin compounds from the reaction mixture and this problem complicates the work-up. Therefore, substantial effort has been devoted to a search for alternative hydrogen atom transfer agents that would also produce efficient chain carrying radicals.

Barton[8] found diphenylsilane to be a good hydrogen atom

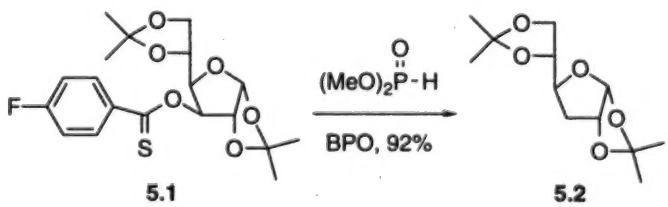
source and in most cases the use of diphenylsilane allows high-yielding transformation of xanthates or thionocarbonates into the corresponding hydrocarbons. Thus, deoxygenation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with diphenylsilane (Scheme 4), triethylborane and air, at room temperature, via the 4-fluorophenylthionocarbonate **4.1**, gave the deoxy product **4.2** in 94% yield.



4.1 **4.2**

Scheme 4

Barton and coworkers[9] have also found that even very inexpensive dialkyl phosphites can be used efficiently in radical deoxygenation, as an alternative to tributyltin hydride. For example, when glucofuranose **5.1** was treated with dimethyl phosphite and benzoyl peroxide in refluxing dioxane a 92% yield of **5.2** was obtained.

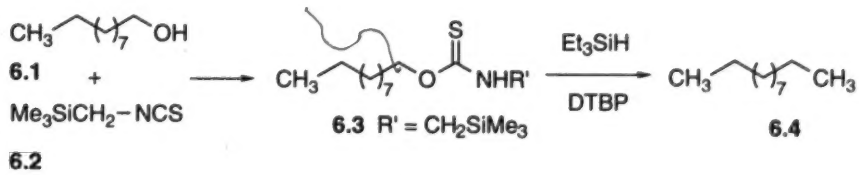


5.1 **5.2**

Scheme 5

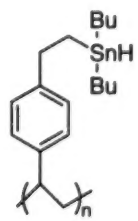
Nishiyama[10] has reported the conversion of alcohols to

thionocarbamates and then reduction with triethylsilane to be a very practical method for the deoxygenation of alcohols. In one example (Scheme 6), thiocarbamate **6.3** was made in 80% yield by treating alcohol **6.1** with isothiocyanate **6.2**. When **6.3** was refluxed in benzene with triethylsilane in the presence of a catalytic amount (10 mol%) of di-*t*-butyl peroxide, the deoxygenated product **6.4** was formed efficiently (88% yield).



Scheme 6

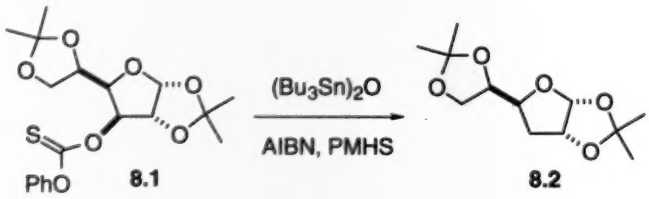
Although some alternatives to tributyltin hydride have been found for the deoxygenation process, none is as versatile as the tin hydride. Therefore efforts have been made for reducing the amounts of toxic tin residues in deoxygenation reactions. Neumann[11] developed the polystyrene-supported di-*n*-butyltin hydride reagent **7.1** which has the ability of being quantitatively regenerated for multiple use.



7.1

Scheme 7

Fu[12] has developed a process in which tributyltin hydride is employed as a catalyst in conjunction with an innocuous stoichiometric reductant, polymethylhydrosiloxane (PMHS). $(Bu_3Sn)_2O$ was used as a precatalyst which, in the presence of PMHS, generates Bu_3SnH *in situ*. Thus, treatment of compound **8.1** with $(Bu_3Sn)_2O$, PMHS (5 equiv.) and AIBN at reflux in toluene provided the desired compound **8.2** efficiently (75%) (Scheme 8).



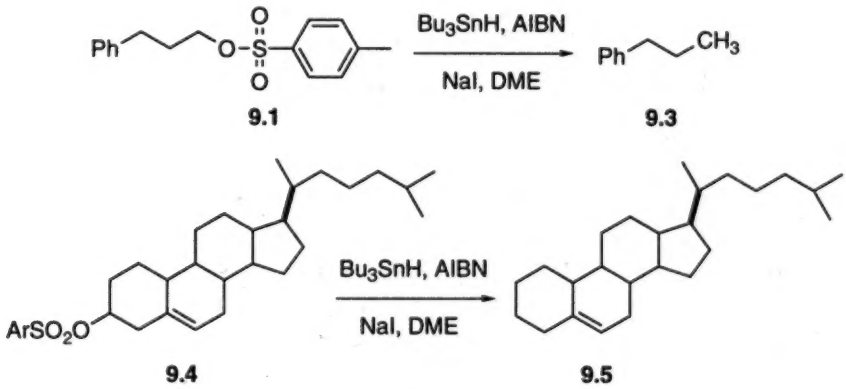
Scheme 8

Recently, Dumartin and coworkers[13] have further improved this reaction by using an insoluble polymer-supported tin hydride in a catalytic amount. Instead of PMHS, a less bulky trimethoxysilane was used as reductant; this can freely diffuse through the cavities of the polystyrene support. The yields obtained from this reaction were comparable to those obtained by Fu (Scheme 8).

B. Other Radical Deoxygenation Processes

The relatively high temperature requirements for stannane-induced deoxygenation of thiocarbonyl derivatives of primary alcohols often is a problem in synthetic chemistry.

Ueno[14] has developed a simple solution to this, in which the alcohol is converted into the *p*-toluenesulfonate and then into its iodide, which is then reduced by tin hydride. This one pot reaction gives excellent yields for primary alcohols, and even secondary alcohols are deoxygenated in useful yields. Thus a toluenesulfonyl derivative of a primary alcohol **9.1** was deoxygenated to **9.3** in 99% overall yield. Cholest-5-ene (**9.5**) was obtained in 64% yield.

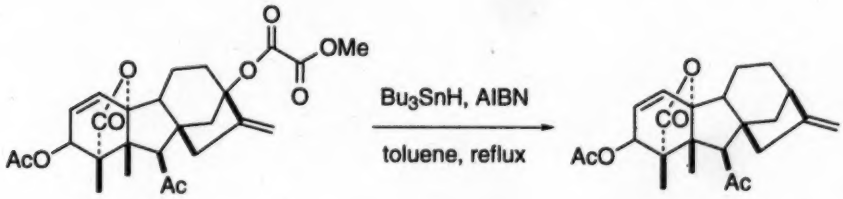


9.1 **9.3** **9.4** **9.5**

Scheme 9

McMillan and coworkers[15] have reported a method for selective deoxygenation of tertiary and allylic alcohols via their mixed methyl oxalate esters. They found that these oxalyl esters are easy to prepare in comparison to the corresponding thiocarbonate and thiobenzoate derivatives used in Barton deoxygenation. These oxalates react with tributyltin hydride in the presence of AIBN as the initiator, generally in refluxing toluene. Selective deoxygenation is possible since the esters from primary alcohols do not suffer

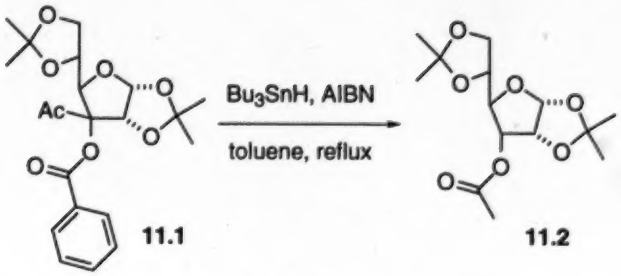
alkyl-oxygen bond homolysis. Thus, methyl oxalyl ester **10.1** gave the deoxygenated product **10.2** in 65% yield.



10.1 **10.2**

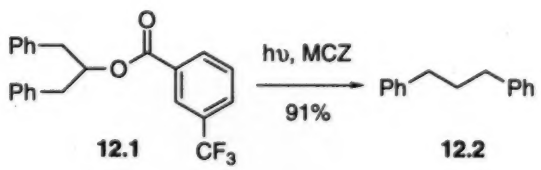
Scheme 10

Owing to the easy availability of benzoates, the deoxygenation of alcohols with tributyltin hydride via these derivatives seems a very attractive proposition. However, under normal circumstances benzoate esters are totally inert to reduction by tributyltin hydride. A very specific exception to this is found in the case of several α-acetyl branched tertiary benzoates of carbohydrates. The effectiveness of this particular reaction is due to a combination of several factors: the formation of a tertiary radical which is also adjacent to a carbonyl group and the presence of additional β-oxygen atoms in the carbohydrate. The furanose **11.1** provides an example of this method; it was deoxygenated[16] to **11.2** in 80% yield.



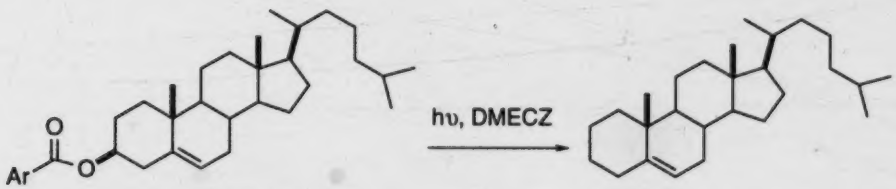
Scheme 11

A practical method for selective deoxygenation of secondary alcohols via benzoates by the use of photosensitized electron transfer reaction has been reported by Saito and coworkers.[17] An advantage of the photodeoxygenation over the Barton and related deoxygenation reactions is that toxic tin species are avoided. In addition, the deoxygenation is carried out at room temperature or below, and benzoyl derivatives are attractive due to their easy synthetic access under mild and neutral conditions. Thus, irradiation of a 10:1 THF-water solution of *m*-(trifluoromethyl)benzoate **12.1** and a photosensitizer, *N*-methylcarbazole, through a Pyrex filter with a high pressure mercury lamp gave 1,3-diphenylpropane **12.2** in 91% yield (Scheme 12).



Scheme 12

Later, Rizzo[18] reported a similar procedure with 3,6-dimethyl-9-ethylcarbazole as a new and improved photosensitizer for such reactions. A number of secondary alcohols have been deoxygenated successfully, with yields in the range 51-92%. In one such example, cholesterol derivatives **13.1** and **13.2** were deoxygenated to **13.3** in 92 and 90% yield, respectively.

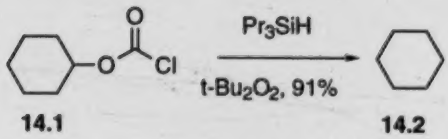


13.1 Ar = m-CF_3C_6H4
13.2 Ar = C_6H_5

13.3

Scheme 13

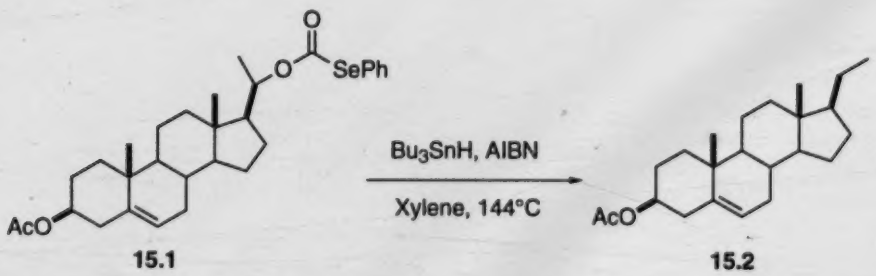
Deoxygenation of alcohols via their chloroformate or selenocarbonate derivatives has also been reported.[2] In the case of chloroformate derivatives, trialkylstannane was found to give side products and thus only trialkylsilanes could be used as hydrogen donors. Since the silane reduction of chloroformates requires homolysis of both a relatively strong carbon-chlorine and silicon-hydrogen bonds for chain propagation, a relatively large excess of initiator is required, together with elevated temperatures. The deoxygenation of alcohols via chloroformates is thus limited to simple primary and secondary alcohols. Compound **14.1** represents a typical example; it was deoxygenated[19] in excellent yield (Scheme 14).



14.1 **14.2**

Scheme 14

Phenylselenocarbonates, prepared from chloroformates and selenophenol, can be reduced to hydrocarbons, sometimes in very good yield, with tributyltin hydride. Here also, however, best yields of alkane are ensured by conducting the reaction at high temperatures. In this way decarboxylation of the alkoxycarbonyl radical ROCO• is assured and competing hydrogen atom capture to give formate esters is minimized. The selenocarbonate **15.1** was deoxygenated in refluxing xylene to afford a 90% yield of the deoxygenated product **15.2** (Scheme 15).

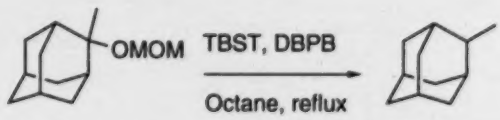


15.1 **15.2**

Scheme 15

Although chloroformate and selenocarbonate derivatives can be prepared in good yields from the corresponding primary and secondary alcohols, yields are often poor for tertiary alcohols.

Recently, Roberts[20] has reported the deoxygenation of tertiary alcohols by heating their MOM ethers in the presence of a peroxide as initiator and a thiol catalyst. The yields were excellent. In one such example (Scheme 16), when the methoxymethyl ether of 2-methyl-2-adamantanol (**16.1**) was treated with tri-*t*-butoxysilanethiol (TBST) and 2,2-di-*t*-butylperoxybutane (DBPB) in refluxing octane, an 87% yield of 2-methyladamantane **16.2** was obtained.



16.1 **16.2**

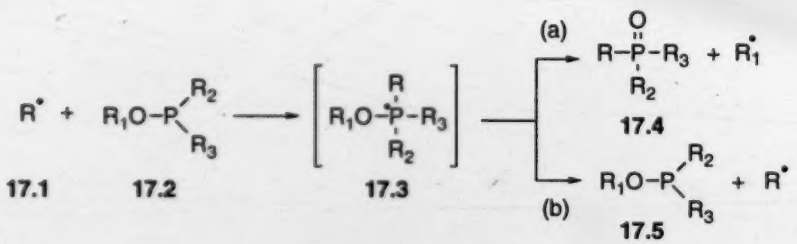
Scheme 16

C. Conclusions

Deoxygenation of alcohols by radical methods is a synthetically very useful process. However, so far the only general process is the Barton reaction, which itself has some limitations, particularly in the deoxygenation of hindered alcohols. Development of an alternate general method for deoxygenation of alcohols would be a valuable contribution in synthetic chemistry.

II. Results and Discussion

As discussed in the previous section there certainly is a need for an alternative procedure for the deoxygenation of alcohols. Our approach to this process was based on the chemistry of phosphorus-centered radicals. It is reported in the literature[21] that alkyl or aryl radicals readily react with trivalent phosphorus compounds generating an intermediate phosphoranyl radical[22] **17.3** (Scheme 17). If an alkoxy group is already attached to the phosphorus, then a β-scission (path **a**, Scheme 17) of the intermediate radical would give an oxidized phosphorus compound **17.4** and an alkyl radical.

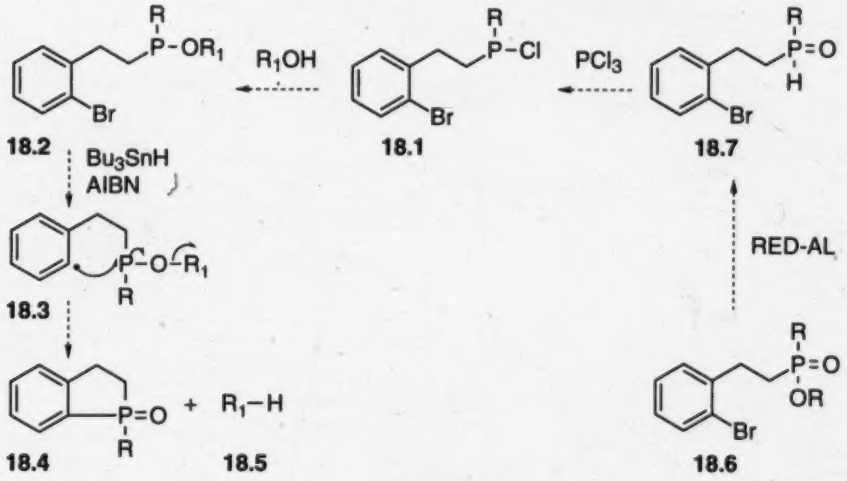


Scheme 17

Although in principle, either reaction (a) or (b) can occur, the one leading to the oxidized phosphorus compound, i.e. reaction (a), is the most frequently encountered,[21,22] as it leads to a stable phosphorus-oxygen double bond. However, this chemistry has not been modified for use as a radical deoxygenation process.

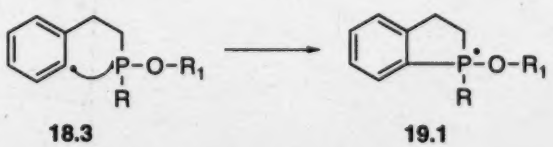
We felt that an intramolecular version of the above

reaction should constitute a useful radical deoxygenation process. We then decided, therefore, to prepare a trivalent phosphorus compound such as **18.1** (Scheme 18), which would then be coupled with various alcohols to give compounds **18.2**. The latter would then be treated with a stannane and an initiator to obtain the deoxygenated product **18.5.**



Scheme 18

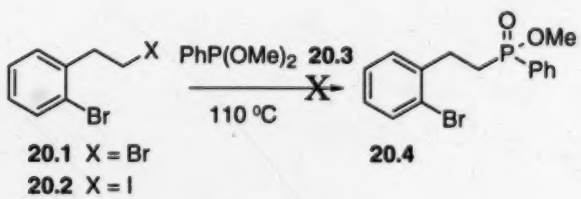
The intermediate phosphoranyl radical[22] **19.1** (Scheme 19), generated in this process, is known to be better stabilized by the presence of an adjacent phenyl group, thus it was necessary to use the phenyl group and the derived aryl radical for optimum efficiency.



Scheme 19

Since it was difficult to prepare a trivalent phosphorus compound of type **18.1** directly, we decided to start its synthesis from a phosphorus pentavalent compound, such as **18.6**, which would then be converted into the trivalent species in two steps, as shown in Scheme 18.

However, the preparation of compounds of type **18.6** was itself found to be rather difficult. The most popular way to synthesize this type of compound is by the Arbuzov reaction[23] of the corresponding halide with a phosphorus trivalent compound. However, in one such attempt along these lines (Scheme 20), heating[24] dimethylphenyl phosphonite **20.3**[25] with bromide **20.1**[26] or with the corresponding iodide **20.2**[27] at 110 °C did not produce the desired product; only a very polar mixture was isolated, and we were unable to identify the components.



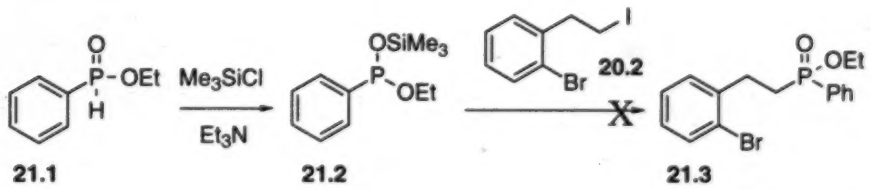
20.1 X = Br
20.2 X = I

20.4

Scheme 20

This reaction would have allowed us to make the substrate with a phenyl substituent attached to the phosphorus, so as to provide extra stabilization to the intermediate phosphoranyl radical, as discussed above (Scheme 19).

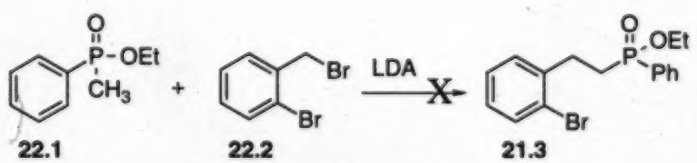
We made several other attempts to make compounds of type **21.3**. The reaction of **21.2** with iodide **20.2**[27] did not produce the desired product **21.3**, even though related reactions have been reported.[28] Thus when phosphinate **21.1**[29] was treated with Me_3SiCl (1.1 equiv.) and Et_3N (1.1 equiv.), followed by the iodide **20.2** (1 equiv.), only the starting iodide was recovered (Scheme 21). Although we took precautions to exclude air, it is possible that the phosphorus reagent was oxidized *in situ*, and would therefore not be nucleophilic.



21.1 **21.2** **21.3**

Scheme 21

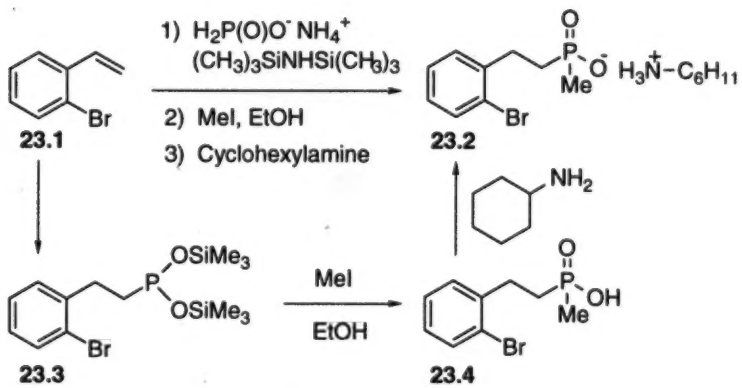
Reaction of **22.1**[30] with LDA and *o*-bromobenzyl bromide was also not successful (Scheme 22), despite the existence of some precedent.[28] When phosphinate **22.1** was treated with LDA (1.2 equiv.) followed by dibromide **22.2** (1 equiv.), the starting bromide **22.2** was very largely recovered.



22.1 **22.2** **21.3**

Scheme 22

However, the corresponding substrate with a methyl substituent **23.2** (Scheme 23) could be easily made[31] by heating the *o*-bromostyrene with ammonium hypophosphite (2.2 equiv.) in the presence of hexamethyldisilazane (4.5 equiv.) at 125°C, followed by addition of iodomethane (Scheme 23). This compound was isolated and characterized as its cyclohexylamine salt.

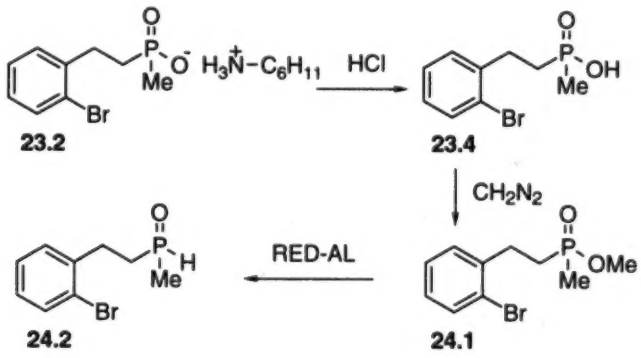


Scheme 23

The intermediate in this type of reaction is proposed[31] to be a bis-silylated compound **23.3** (Scheme 23), which then undergoes Arbuzov rearrangement[23] in the presence of iodomethane to afford the corresponding phosphinic acid **23.4**. The acid was then converted into the cyclohexylamine salt **23.2**.

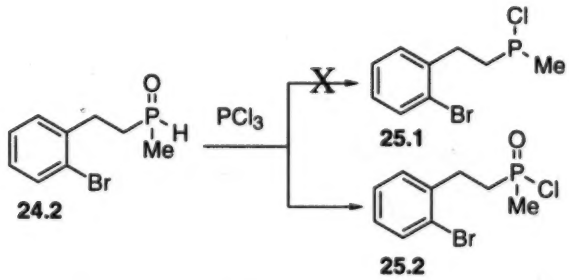
The cyclohexylamine salt was treated with hydrochloric acid to get the phosphinic acid **23.4** (Scheme 24), which was then converted into the corresponding methyl ester **24.1** in high yield by treatment with ethereal diazomethane (Scheme

24). Reduction of **24.1** with 1.3 equivalents of RED-AL then resulted in the phosphinous acid **24.2**.



Scheme 24

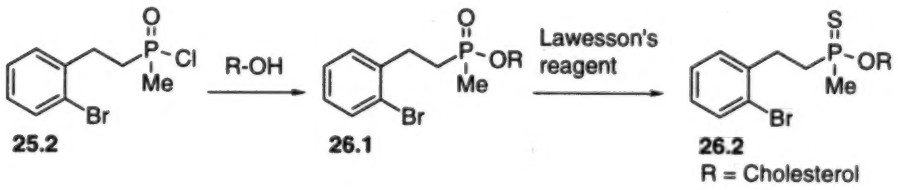
However, conversion of **24.2** into the trivalent chloro compound **25.1** was not successful (Scheme 25). Even with our best attempts at strict exclusion of air, only the oxidized pentavalent chloro compound **25.2** was isolated.



Scheme 25

We then decided to use this pentavalent phosphorus compound (**25.2**), and convert it, as described below, into the trivalent species *in situ*, during the radical deoxygenation. Compound **25.2** was coupled with cholesterol (Scheme 26) to

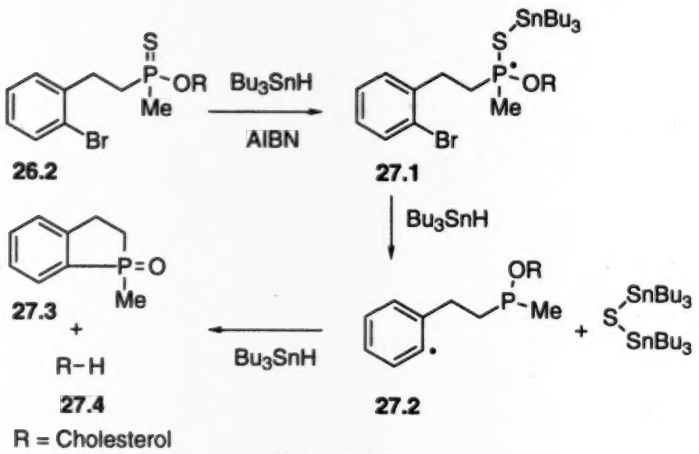
produce **26.1**, which was then converted into the corresponding phosphinothioate **26.2** by means of Lawesson's reagent (Scheme 26).



25.2 **26.1** **26.2**
R = Cholesterol

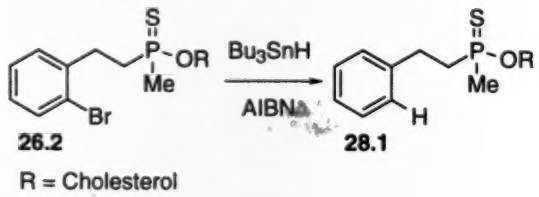
Scheme 26

In principle, when compound **26.2** is treated with an excess of Bu_3SnH in the presence of AIBN, the tributyltin radical is expected to add to the sulfur of the P=S bond, generating **27.1**. This might expel the sulfur unit, which could also become detached by attack by another stannyl radical. Further reaction with the stannane would give the aryl radical **27.2** (Scheme 27). The aromatic radical should then react with the trivalent phosphorus to afford the desired deoxygenated product **27.4**.



Scheme 27

However, when **26.2** was subjected to the radical conditions, using 3.5 equivalent of Bu_3SnH, a quantitative yield of reduced product **28.1** was obtained.



Scheme 28

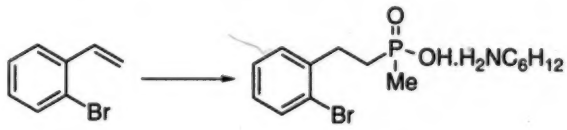
Conclusions

Although the principles described above for using phosphorus radicals to effect the deoxygenation of alcohols appear sound, the sensitivity of some of the phosphorus intermediates to hydrolysis and/or air has probably thwarted our attempts to demonstrate the process. However, further work to overcome these problems is continuing in this laboratory.

III. Experimental Section

General Procedures. The same general procedures were used as described in part 1 of this thesis.

[2-(2-Bromophenyl)ethyl]methylphosphinic Acid Salt with Cyclohexylamine (23.2).

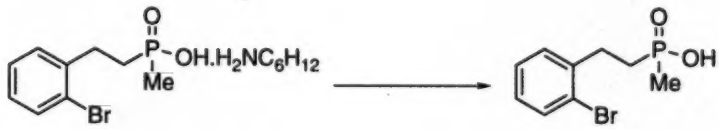


23.1 **23.2**

A mixture of 2-bromostyrene **23.1**[32] (3.5 mL, 13 mmol), ammonium hypophosphite[33] [$H_2P(O)O^-NH_4^+$] (2.50 g, 29.8 mmol) and $(Me_3Si)_2NH$ (7.5 mL, 61 mmol) was stirred at 125 °C for 5 h, and then cooled to 40 °C. MeI (2.0 mL, 6.2 mmol) was added dropwise and the resulting mixture was stirred for 1 h at 45 °C. EtOH (25 mL) was added, and the mixture was refluxed for 30 min, and then evaporated. The residue was dissolved in PhH (25 mL) and washed with water (2 x 10 mL). The organic solution was evaporated, and the residue was dissolved in a mixture of EtOH (3.5 mL) and cyclohexylamine (3.4 mL, 30 mmol). The solution was evaporated immediately and the residue was recrystallized from 8:3 Et_2O-acetone to give **23.2** (2.58 g, 54%) as a crystalline solid: mp 168-175 °C; FTIR (CH_2Cl_2 cast) 2935, 2857, 2190, 1632, 1566 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 0.96-1.51 [m, including a doublet at δ

1.24 (J = 15.0 Hz), 8 H in all], 1.51-1.61 (m, 1 H), 1.62-1.92 (m, 4 H), 2.01-2.21 (m, 2 H), 2.74-3.04 (m, 3 H), 6.84-7.58 (m, 4 H), 7.93-9.42 (br s, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 4.3 (s'), 16.7 (**C**H_3 signal split into d, J = 90 Hz), 24.8 (t'), 25.0 (t'), 30.9 (t'), 33.5 (t'), 49.9 (d'), 127.6 (d'), 129.6 (d'), 132.8 (d'),141.8 (quaternary **C** signal split into d, J = 15 Hz); exact mass (electrospray) m/z calcd for $C_{15}H_{26}{}^{79}BrNNaO_2P$ (M + Na) 362.0884, found 362.0886.

[2-(2-Bromophenyl)ethyl]methylphosphinic Acid (23.4).



23.2 **23.4**

Hydrochloric acid (1 N, 15 mL) was added to a stirred solution of compound **23.2** (2.5 g, 6.9 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 30 min and the mixture was then extracted with CH_2Cl_2 (3 x 10 mL). Evaporation of the solvent gave **23.4** (1.80 g, 99%) as a colorless oil, which was used for the next step without purification.

Methyl [2-(2-Bromophenyl)ethyl]methylphosphinate (24.1).

23.4 **24.1**

Ethereal CH_2N_2 was added dropwise to a stirred solution of **23.4** (1.76 g, 6.72 mmol) in Et_2O (15 mL) until the light yellow color of CH_2N_2 persisted. Compound **23.4** does not dissolve readily in Et_2O, however it dissolved completely after a few drops of diazomethane had been added. The solution was stirred overnight, and then evaporated to obtain pure (^1H NMR) **24.1** (1.81 g, 98%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3443, 3056, 2985, 1198, 1099, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.45 (d, J = 15.0 Hz, 3 H), 1.92-2.21 (m, 2 H), 3.01 (q, J = 6.0 Hz, 2 H), 3.71 (d, J = 12 Hz, 3 H), 7.03-7.66 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 13.3 (**C**H_3 signal split into d, J = 91.6 Hz), 29.16 (**C**H_2 signal split into d, J = 5.1 Hz), 29.5 (**C**H_2 signal split into d, J = 90 Hz), 50.89 (**C**H_3 signal split into d, J = 6.1 Hz), 123.9 (s'), 127.7 (d'), 128.2 (d'), 130.1 (d'), 130.21 (d'), 130.23 (d'), 132.9 (d'), 139.94 (quaternary **C** signal split into d, J = 15.2 Hz); ^{31}P NMR ($CDCl_3$, 81.02 MHz) δ 55.01; exact mass m/z calcd for $C_{10}H_{14}{}^{79}BrO_2P$ (M + H) 276.9993, found 276.9988.

[2-(2-Bromophenyl)ethyl]methylphosphinous acid (24.2).

24.1 **24.2**

RED-AL (1.52 mL, 10.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **24.1** (2.3 g, 8.3 mmol) in THF (15 mL). Stirring at 0 °C was continued for 2 h. A few drops of hydrochloric acid (1 N) were then added, and the resulting precipitate was filtered off. Evaporation of the filtrate and flash chromatography of the residue over silica gel (4 x 30 cm), using 50% EtOAc-hexane, gave **24.2** (1.71 g, 83%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, *J* = 10 Hz, 3 H), 1.64-1.88 (m, 2 H), 2.68-3.14 (m, 3 H), 6.93-7.61 (m, 4 H).

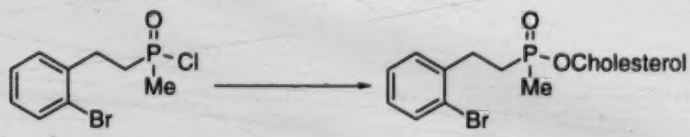
[2-(2-Bromophenyl)ethyl]methylphosphinic Acid Chloride (25.2).

24.2 **25.2**

PCl_3 (900 mg, 6.55 mmol) was added in one portion with stirring to **24.2** (400 mg, 1.62 mmol), and the mixture was stirred for 4 h (N_2 atmosphere). The resulting yellow, gummy solid was then filtered off from the supernatant liquid

(protection from moisture). Evaporation of the filtrate gave **25.2** (322 mg, 71%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) 1.57 (d, J = 18.4 Hz, 3 H), 2.11-2.47 (m, 2 H), 2.88-3.25 (m, 2 H), δ 7.01-7.71 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 13.58 (**C**H_3 signal split into d, J = 90 Hz), 28.35 (**C**H_2 signal split into d, J = 8 Hz), 29.28 (**C**H_2 signal split into d, J = 90 Hz), 124.0 (s'), 127.9 (d'), 128.6 (d'), 130.5 (d'), 133.0 (d'), 139.13 (quaternary **C** signal split into d, J = 15 Hz); ^{31}P NMR ($CDCl_3$, 81.02 MHz) δ 62.6.

5α-Cholesteryl [2-(2-Bromophenyl)ethyl]methylphosphinate (26.1).



25.2 **26.1**

Pyridine (110 mg, 1.39 mmol) was added to a stirred solution of **25.2** (300 mg, 1.07 mmol) and cholesterol (500 mg, 1.29 mmol) in THF (10 mL). Stirring was continued overnight and the solvent was evaporated. The residue was dissolved in CH_2Cl_2 (15 mL) and the solution was washed with water (2 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 34 cm), using 80% EtOAc-hexane, gave **26.1** (521 mg, 77%) as a crystalline solid: mp 173-176 °C; FTIR (CH_2Cl_2 cast) 2938, 2866, 1469, 1298, 1133 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 200 MHz) δ 0.66 (s, 3 H), 0.76-2.14 (m,

43 H), 2.32-2.50 (m, 2 H), 2.92-3.03 (m, 2 H), 4.18-4.32 (m, 1 H), 5.31-5.4 (m, 1 H), 7.01-7.68 (m, 4 H); ^{13}C NMR (CD_2Cl_2, 50.3 MHz) δ 11.9 (q'), 15.06 (CH_3 signal split into d, J = 90 Hz), 18.9 (d' or q'), 19.5 (d' or q'), 21.4 (s' or t'), 22.7 (d' or q'), 22.9 (d' or q'), 24.2 (s' or t'), 24.6 (s' or t'), 28.4 (d' or q'), 28.6 (s' or t'), 29.6 (s' or t'), 30.1 (s' or t'), 30.8 (s' or t'), 31.9 (s' or t'), 32.2 (d' or q'), 32.3 (s' or t'), 36.2 (d' or q'), 36.5 (s' or t'), 36.8 (s' or t'), 37.4 (s' or t'), 39.8 (s' or t'), 40.1 (s' or t'), 41.2 (s' or t'), 42.6 (t'), 50.5 (d'), 56.5 (d'), 57.1 (d'), 75.2 (d'), 75.3 (d'), 123.0 (d'), 124.4 (s'), 128.2 (d'), 128.5 (d'), 130.7 (d'), 133.3 (d'), 140.3 (s'), 140.8 (s'), 141.1 (s'); ^{31}P NMR ($CDCl_3$, 161.98 MHz) δ 52.06; exact mass (electrospray) *m/z* calcd for $C_{36}H_{56}{}^{79}BrNaOP$ (M + Na) 653.3099, found 653.3105.

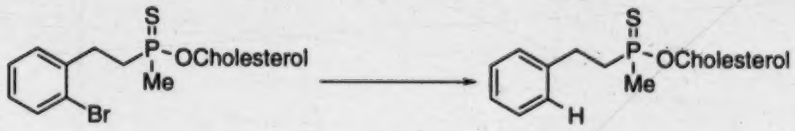
***O*-5α-Cholesteryl [2-(2-Bromophenyl)ethyl]methylphosphinothioate (26.2).**

26.1 **26.2**

Lawesson's reagent (3.42 g, 8.41 mmol) was added to a stirred solution of **26.1** (3.82 g, 6.05 mmol) in PhMe (20 mL), and the resulting suspension was refluxed for 8 h. Evaporation of the solvent and flash chromatography of the

residue over silica gel (4 x 34 cm), using 5% EtOAc-hexane, gave **26.2** (3.41 g, 87%) as a crystalline solid: FTIR (CH_2Cl_2 cast) 2937, 1469, 1380, 1291, 881 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.66 (s, 3 H), 0.71-2.49 (m, 45 H), 2.82-3.21 (m, 2 H), 4.18-4.50 (m, 1 H), 5.33-5.48 (m, 1 H), 7.03-7.68 (m, 4 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 11.9 (q'), 18.8 (d' or q'), 19.4 (d' or q'), 21.14 (s' or t'), 21.15 (s' or t'), 22.67 (d' or q'), 22.85 (d' or q'), 22.88 (d' or q'), 22.9 (d' or q'), 23.4 (d' or q'), 23.5 (d' or q'), 23.9 (s' or t'), 24.4 (s' or t'), 28.1 (d' or q'), 28.3 (s' or t'), 29.9 (s' or t'), 30.0 (s' or t'), 30.2 (s' or t'), 30.3 (s' or t'), 30.4 (s' or t'), 31.94 (d' or q'), 31.98 (s' or t'), 35.9 (d' or q'), 36.3 (s' or t'), 36.5 (s' or t'), 36.6 (s' or t'), 36.7 (s' or t'), 37.02 (s' or t'), 37.03 (s' or t'), 37.21 (s' or t'), 37.24 (s' or t'), 39.6 (s' or t'), 39.8 (s' or t'), 40.4 (s' or t'), 40.5 (s' or t'), 40.70 (s' or t'), 40.73 (s' or t'), 42.4 (t'), 50.0 (d'), 56.2 (d'), 56.7 (d'), 75.6 (d'), 75.7 (d'), 122.7 (d'), 122.8 (d'), 124.1 (s'), 127.7 (d'), 128.1 (d'), 130.3 (d'), 130.4 (d'), 132.88 (d'), 139.47 (quaternary **C** signal split into d, J = 3.8 Hz), 139.9 (quaternary **C** signal split into d, J = 6.5 Hz); ^{31}P NMR (CD_2Cl_2, 81.02 MHz) δ 93.92; exact mass (electrospray) m/z calcd for $C_{36}H_{56}{}^{79}BrNaOPS$ (M + Na) 669.2870, found 669.2876.

***O*-5α-Cholesteryl (2-Phenylethyl)methylphosphinothioate (28.1).**



26.2 **28.1**

The general procedure for radical cyclization was followed, using **26.2** (182.8 mg, 0.2829 mmol) in PhMe (40 mL), Bu_3SnH (288 mg, 0.989 mmol) in PhMe (10 mL), and AIBN (14 mg, 0.085 mmol) in PhMe (10 mL). Flash chromatography of the residue over silica gel (1.7 x 28 cm), using 5% EtOAc-hexane, gave **28.1** (156 mg, 97%) as a crystalline solid: mp 135-139 °C; FTIR (CH_2Cl_2 cast) 3026, 2866, 1603, 880, 830 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.62-2.45 (m, 48 H), 2.85-3.04 (m, 2 H), 4.34-4.42 (m, 1 H), 5.33-5.41 (m, 1 H),7.12-7.35 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 11.9 (q'), 18.8 (d' or q'), 19.4 (d' or q'), 21.1 (s' or t'), 22.7 (d' or q'), 22.9 (d' or q'), 23.5 (d' or q'), 23.6 (d' or q'), 23.9 (s' or t'), 24.4 (s' or t'), 28.1 (d' or q'), 28.3 (s' or t'), 29.0 (s' or t'), 30.1 (s' or t'), 30.2 (s' or t'), 30.4 (s' or t'), 31.93 (d' or q'), 31.97 (s' or t'), 35.9 (d' or q'), 36.3 (s' or t'), 36.5 (s' or t'), 37.0 (s' or t'), 38.2 (s' or t'), 38.3 (s' or t'), 38.83 (s' or t'), 38.9 (s' or t'), 39.6 (s' or t'), 39.7 (s' or t'), 40.43 (s' or t'), 40.46 (s' or t'), 40.68 (s' or t'), 40.7 (s' or t'), 42.4 (t'), 50.0 (d'), 56.1 (d'), 56.7 (d'), 75.6 (d'), 122.82 (d'), 122.83 (d'), 126.3 (d'), 128.1 (d'), 128.2 (d'), 128.5 (d'), 139.5 (s'), 140.6 (quaternary **C** signal split into d, J = 15 Hz); ^{31}P NMR ($CDCl_3$,

81.02 MHz) δ 94.47; exact mass *m/z* calcd for $C_{36}H_{57}NaOPS$ (M + Na) 591.3765, found 591.3772.

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33 Ammonium hypophosphite was made by adding solid $(NH_4)_2CO_3$ to hypophosphorous acid, until the CO_2 evolution ceased. Excess of $(NH_4)_2CO_3$ was filtered and the liquid evaporated (water pump, 40 °C). The resulting solid was recrystallized from ethanol, filtered and vacuum dried.

mp 170-174 °C.

APPENDIX

In further attempts to shed more light on the mechanism, I carried out a number of control experiments, after the main body of the Thesis had been submitted.

The simple *O*-trityloxime derived from benzaldehyde was recovered (95%) unchanged after being subjected to our best cyclization conditions.

As mentioned earlier, the *O*-trityloxime **70.3**, failed to cyclize under our usual conditions, and so we tried to effect cyclization using $(Me_3Si)_3SiH$ (THF, ABC, *i*-Pr_2NEt) and, in a separate experiment, using *N*-ethylpiperidinium hypophosphite (THF). In the former case, 98% of the starting material was recovered, in the later case 82%. The result was not significantly different when the silane experiment was repeated in the absence of Hünig's base (93% recovery).

The use of *N*-ethylpiperidinium hypophosphite in THF was also tried with *O*-trityloxime **56.2**, which does cyclize under our usual conditions, but in this case 66% of the starting material was recovered. At this point, the quality of our *N*-ethylpiperidinium hypophosphite was checked by carrying out the reduction of 1-bromoadamantane to adamantane.

We then performed a more rigorous test: A mixture of **56.2** and 1-bromoadamantane was treated with *N*-ethylpiperidinium hypophosphite (THF). In this experiment additional AIBN was added. Some of the starting oxime (**56.2**) (25%), some of the desired cyclization product (**61.1**) (32%),

bromoadamantane, and adamantane were formed. We conclude that *N*-ethylpiperidinium hypophosphite is not a very effective reagent for our cyclizations. This view was confirmed by using the phosphorus reagent to effect cyclization of **70.7**. The desired product (**70.8**) was obtained in 41% yield; when we had used Bu_3SnH, the yield was 61%.

A mixture of the *O*-trityloxime **70.3** and the *O*-benzyloxime **70.7** was also treated with *N*-ethylpiperidinium hypophosphite in the presence of ABC in THF. NMR analysis of the reaction mixture indicated that both starting materials were present and were the main components of the mixture.

We have also subjected the *O*-trityloxime **70.3** to exhaustive reduction with Bu_3SnH, using ABC in refluxing PhMe, and obtained Ph_3CH (ca. 39%), but we did not identify the product(s).

When cyclization of **56.2** was tried in the absence of initiator, the starting material was recovered unchanged. Finally, cyclization of **56.2**, allowed us to identify Ph_3CH (56%).

Conclusion

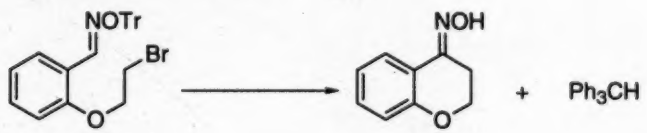
The above experiments do not provide an explanation for the fact that cyclization of some *O*-trityloximes proceeds in excellent yield, while others do not appear to give the cyclization products. The isolation of Ph_3CH, and the necessity of the initiator, indicate that the reactions are

free radical chain processes. Future work in this laboratory will involve the preparation of authentic samples of the cyclization products expected from the compounds that appear not to cyclize, so that even small amounts of cyclization products could then be detected. We will also prepare an *O*-trityloxime with an α-oxygen substituent, but no other substituents on the chain, in order to establish if an oxygen substituent adjacent to the oxime function is important.

Experimental section

General Procedures. The same procedures were used as described in Part 2 of this thesis.

Isolation of Triphenylmethane.



56.2 **61.1**

Radical cyclization was carried out using **56.2** (275 mg, 0.566 mmol) in THF (35 mL), Bu_3SnH (660 mg, 2.26 mmol) in THF (7 mL), ABC (14 mg, 0.056 mmol) in THF (7 mL), and *i*-Pr_2NEt (360 mg, 2.83 mmol). Flash chromatography of the residue over silica gel (1.7 x 18 cm), which was repeated three times, using petroleum ether (bp 40-60 °C) gave triphenylmethane (78 mg, 56%). The cyclized oxime **61.1** was

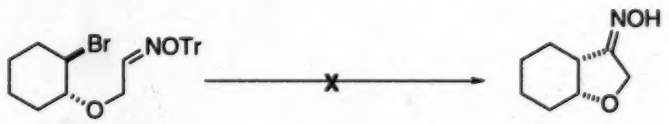
formed (TLC), but was not isolated in this experiment.

Treatment of Benzaldehyde *O*-(Triphenylmethyl)-oxime (75.1) with Tributyltin Hydride.

75.1

The general procedure for radical cyclization was followed, using **75.1** (180 mg, 0.51 mmol) in THF (30 mL), Bu_3SnH (577 mg, 1.98 mmol) in THF (7 mL), AIBN (12 mg, 0.053 mmol), and *i*-Pr_2NEt (260 mg, 198 mmol). Flash chromatography of the residue over silica gel (1.7 × 20 cm), using 5% EtOAc-hexane, gave recovered **75.1** (173 mg, 95%) as a foam. The material was identified by its ^1H NMR spectrum.

Treatment of trans-2-[2-Bromocyclohexyl)oxy]-acetaldehyde *O*-(Triphenylmethyl)oxime (70.3) with Tris(trimethylsilyl) silane.



70.3

The general procedure for radical cyclization was followed, using **70.3** (162 mg, 0.338 mmol) in THF (20 mL), $(Me_3Si)_3SiH$

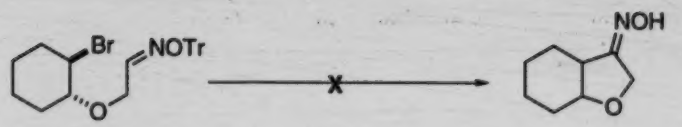
(168 mg, 0.677 mmol) in THF (4 mL), ABC (8 mg, 0.03 mmol) in THF (4 mL) and *i*-Pr_2NEt (175 mg, 1.36 mmol). Flash chromatography of the residue over silica gel (1.7 × 25 cm), using 5% EtOAc-hexane, gave recovered **70.3** (159 mg, 98%) as a foam.

Treatment of Trans-2-[2-Bromocyclohexyl)oxy]-acetaldehyde *O*-(Triphenylmethyl)oxime (70.3) with *N*-ethylpiperidinium Hypophosphite.

70.3

AIBN (22 mg, 0.13 mmol) in THF (4 mL) was added slowly (over ca 3 h) to a refluxing solution of *N*-ethylpiperidinium hypophosphite (610 mg, 3.34 mmol) and **70.3** (160 mg, 0.334 mmol) in THF (15 mL). Refluxing was continued for 24 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.7 × 20 cm), using 5% EtOAc-hexane, gave recovered **70.3** (131 mg, 82%) as a foam.

Treatment of Trans-2-[2-Bromocyclohexyl)oxy]-acetaldehyde *O*-(Triphenylmethyl)oxime (70.3) with Tris(trimethylsilyl) silane in the Absence of a Base.



70.3

The general procedure for radical cyclization was followed, using **70.3** (182 mg, 0.381 mmol) in THF (12 mL), $(Me_3Si)_3SiH$ (190 mg, 0.764 mmol) in THF (3 mL) and ABC (10 mg, 0.04 mmol) in THF (3 mL). Flash chromatography of the residue over silica gel (1.7 × 28 cm), using 5% EtOAc-hexane, gave recovered **70.3** (169 mg, 93%) as a foam.

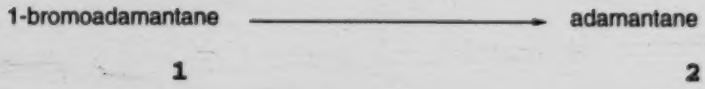
Treatment of 2-(2-Bromoethoxy)benzaldehyde *O*-(Triphenylmethyl)oxime (56.2) with *N*-ethylpiperidinium Hypophosphite.

56.2

AIBN (30 mg, 0.15 mmol) in THF (4 mL) was added slowly (over ca 3 h) to a refluxing solution of *N*-ethylpiperidinium hypophosphite (674 mg, 3.76 mmol) and **56.2** (183 mg, 0.376 mmol) in THF (10 mL). Refluxing was continued for 28 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.7 × 20 cm), using 5% EtOAc-hexane, gave

recovered **56.2** (119.4 mg, 66%) as a foam.

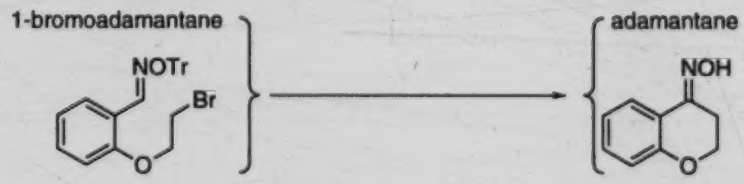
Reduction of 1-Bromoadamantane with *N*-Ethylpiperidinium Hypophosphite.



1 **2**

AIBN (40 mg, 0.22 mmol) in THF (3 mL) was added slowly (over ca 2 h) to a refluxing solution of *N*-ethylpiperidinium hypophosphite (610 mg, 3.34 mmol) and **1** (120 mg, 0.557 mmol) in THF (8 mL). Refluxing was continued for 6 h. The reaction mixture was cooled to room temperature and the solvent was evaporated. The residue was washed through a small pad of silica gel, using petroleum ether (bp 35-60 °C) (100 mL) to afford **2** which was mixed with **1**. No attempt was made to further separate the compounds.

Treatment of a Mixture of 1-Bromoadamantane and 2-(2-Bromoethoxy)benzaldehyde *O*-(Triphenylmethyl)oxime (56.2) with *N*-ethylpiperidinium Hypophosphite.



1 (upper), **56.2** **2** (upper), **61.1**

AIBN (70 mg, 0.37 mmol) in THF (3 mL) was added slowly (3 h) in a refluxing solution of *N*-ethylpiperidinium hypophosphite (995 mg, 5.55 mmol), 1-bromoadamantane (**1**) (122 mg, 0.567 mmol) and **56.2** (174 mg, 0.358 mmol). Refluxing was continued for 18 h. More AIBN (73 mg, 0.44 mmol) in THF (3 mL) was added slowly (over ca 3 h). The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.7 × 30 cm), using first petroleum ether (bp 35-60 °C) (50 mL) and then 5% EtOAc-hexane, gave adamantane (**2**) (mixed with **1**), **61.1** (19 mg, 32%), and recovered **56.2** (43 mg, 25%).

Note that we get cyclization in this experiment, but not in the previous one, using the phosphorus reagent. However, here we have added additional AIBN, and only after the addition was the cyclization observed.

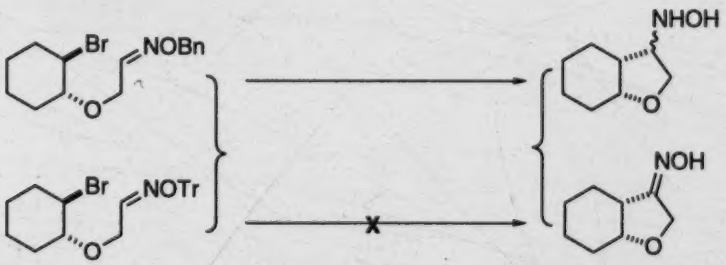
Treatment of Trans-2-[2-Bromocyclohexyl)oxy]-acetaldehyde *O*-(Phenylmethyl)oxime (70.7) with *N*-ethylpiperidinium Hypophosphite.

70.7 **70.8**

ABC (40 mg, 0.16 mmol) in THF (3 mL) was added slowly (over ca 3 h) to a refluxing solution of *N*-ethylpiperidinium hypophosphite (433 mg, 2.42 mmol) and **70.7** (131 mg, 0.406

mmol) in THF (10 mL). Refluxing was continued for 18 h. More ABC (43 mg, 0.18 mmol) in THF (3 mL) was added slowly (over ca 3 h). The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash chromatography of the residue over silica gel (1.7 × 27 cm), using 20% EtOAc-hexane, gave **70.8** (41 mg, 41%).

Treatment of a mixture of trans-2-[2-Bromocyclohexyl)oxy]acetaldehyde *O*-(Phenylmethyl)oxime (70.7) and trans-2-[2-Bromocyclohexyl)oxy]acetaldehyde *O*-(Triphenylmethyl)oxime (70.3) with *N*-ethylpiperidinium Hypophosphite.



70.7 (upper), **70.3** **70.8** (upper)

ABC (111 mg, 0.454 mmol) in THF (5 mL) was added slowly (over ca 4 h) to a refluxing solution of *N*-ethylpiperidinium hypophosphite (1.23 g, 6.8 mmol), **70.7** (233 mg, 0.724 mmol) and **70.3** (200 mg, 0.422 mmol). Refluxing was continued for 16 h. More ABC (43 mg, 0.18 mmol) in THF (4 mL) was added slowly (over 3 h). The reaction mixture was cooled to room temperature and the solvent was evaporated. Flash

chromatography of the residue over silica gel (1.7 × 29 cm), using first 5% EtOAc-hexane, gave an inseparable mixture of compounds, probably (based on tlc and ^{1}H NMR examination) **70.7** and **70.3**) and elution with 15% EtOAc-hexane gave **70.8** (48.2 mg, 27%).

Exhaustive Reduction of trans-2-[2-Bromocyclohexyl)oxy]acetaldehyde *O*-(Triphenylmethyl)oxime (70.3) with Tributyltin Hydride.

70.3

A mixture of **70.3** (165 mg, 0.350 mmol), PhMe (10 mL), Bu_3SnH (502 mg, 1.73 mmol), ABC (33.7 mg, 0.140 mmol) and *i*-Pr_2NEt (183 mg, 1.40 mmol) was refluxed overnight. Examination of the mixture by tlc (silica, 30% EtOAc-hexane) suggested the presence of Ph_3CH. A blue spot (after development with phosphomolybdic acid) was observed, and was reminiscent of the type of spot seen in successful cyclizations. Flash chromatography of the residue over silica gel (1.7 × 28 cm), using first petroleum ether (bp 30-40 °C), gave Ph_3CH (86 mg, 39%). Further development with 30% EtOAc-hexane, gave the material corresponding to the blue spot (mixed with tin-containing species). Attempts to identify this material are in progress.